

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
24 April 2003 (24.04.2003)

PCT

(10) International Publication Number  
**WO 03/033477 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 239/96**,  
487/04, A61K 31/51, A61P 19/02, C07D 471/04 // (C07D  
471/04, 239:00, 221:00) (C07D 487/04, 249:00, 239:00)

SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,  
ZA, ZW.

(21) International Application Number: PCT/EP01/11824

(22) International Filing Date: 12 October 2001 (12.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant (for all designated States except US):  
**WARNER-LAMBERT COMPANY** [US/US]; 201  
Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GAUDILLIERE**,  
**Bernard** [FR/FR]; 28 rue de Zilina, F-92000 Nanterre  
(FR). **JACOBELLI, Henry** [FR/FR]; 65 avenue du  
Général de Gaulle, F-91550 Paray Vieille Poste (FR).

(74) Agent: **HIRSCH, Denise**; Warner-Lambert Company,  
c/o Parke-Davis, Pfizer Global Research & Development,  
Fresnes Laboratories, 3-9 rue de la Loge, B.P. 100,  
F-94265 Fresnes (FR).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI,

(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,  
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,  
TG).

**Declarations under Rule 4.17:**

— as to applicant's entitlement to apply for and be granted  
a patent (Rule 4.17(ii)) for the following designations AE,  
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,  
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI,  
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,  
KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,  
MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE,  
SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,  
ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL,  
SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ,  
MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE,  
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR),  
OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,  
ML, MR, NE, SN, TD, TG)

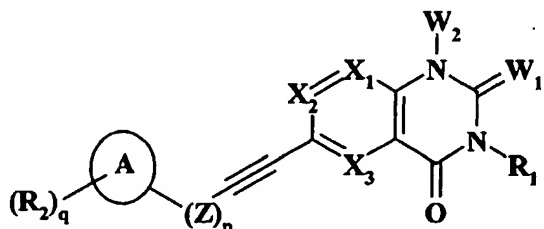
— of inventorship (Rule 4.17(iv)) for US only

**Published:**

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: **ALKYNLATED FUSED RING PYRIMIDINE COMPOUNDS AS MATRIX METALLOPROTEASE-13 INHIBITOR**



optionally substituted, or W<sub>1</sub> and W<sub>2</sub> form together a group of formula -N=X<sub>4</sub>W<sub>3</sub>, as defined in the description, X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> represent N or C optionally substituted, n is 0 to 8, Z represents -CR<sub>12</sub>R<sub>13</sub>, wherein R<sub>12</sub> and R<sub>13</sub> are as defined in the description, A represents a ring system, the groups R<sub>2</sub> represent hydrogen, alkyl, halogen, cyano, nitro, trihalogenoalkyl, -NR<sub>10</sub>R<sub>11</sub>, -OR<sub>14</sub>, -SR<sub>14</sub>, -SOR<sub>14</sub>, -SO<sub>2</sub>R<sub>14</sub>, acyl, -(CH<sub>2</sub>)<sub>k</sub>NR<sub>10</sub>R<sub>11</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>NR<sub>10</sub>R<sub>11</sub>, -(CH<sub>2</sub>)<sub>k</sub>SO<sub>2</sub>NR<sub>14</sub>R<sub>15</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>14</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>14</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>14</sub>R<sub>15</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>14</sub>R<sub>15</sub> and -X<sub>6</sub>-R<sub>16</sub> in which X<sub>5</sub>, k, R<sub>10</sub>, R<sub>11</sub>, R<sub>14</sub>, R<sub>15</sub>, X<sub>6</sub>, and R<sub>16</sub> are as defined in the description, q is 0 to 7; R<sub>1</sub> represents hydrogen, alkyl, alkenyl, alkynyl, or a ring system, and optionally, its optical isomers, N-oxide, and addition salts thereof with a pharmaceutically-acceptable acid or base, and medicinal products containing the same are useful as specific inhibitors of type-13 matrix metalloprotease.

(57) Abstract: A compound selected from those of formula (I) : wherein W<sub>1</sub> represents O, S, or -NR<sub>3</sub> in which R<sub>3</sub> represents hydrogen, alkyl, OH or CN; W<sub>2</sub> represents a group selected from hydrogen, CF<sub>3</sub>, NH<sub>2</sub>, monoalkylamino, dialkylamino, alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkylalkyl, heterocycle, these groups being

(I)

USSN 10/619,663 FILED: 07/15/2003  
DOCKET NO. PC25207A

WO 03/033477 A1

**TITLE OF THE INVENTION**

ALKYNYLATED FUSED RING PYRIMIDINE COMPOUNDS AS MATRIX METALLOPROTEASE-13  
INHIBITOR

**FIELD OF THE INVENTION**

5 The present invention relates to novel alkynylated fused ring pyrimidine compounds which are useful for preparing medicinal products for treating complaints involving a therapy with a matrix metalloprotease-13 (MMP-13) inhibitor. These medicinal products are useful in particular for treating certain inflammatory conditions such as rheumatoid arthritis or osteoarthritis, as well as certain proliferative conditions such as cancers.

**TECHNOLOGICAL BACKGROUND OF THE INVENTION**

10 Matrix metalloproteases (MMPs) are enzymes which are involved in the renewal of extracellular matrix tissue, such as cartilage, tendons and joints. MMPs bring about the destruction of the extracellular matrix tissue, which is compensated for, in a non-pathological physiological state, by its simultaneous regeneration.

15 Under normal physiological conditions, the activity of these extremely aggressive peptidases is controlled by specialized proteins which inhibit MMPs, such as the tissue inhibitors of metalloprotease (TIMPs).

20 Local equilibrium of the activities of MMPs and of TIMPs is critical for the renewal of the extracellular matrix. Modifications of this equilibrium which result in an excess of active MMPs, relative to their inhibitor, induce a pathological destruction of cartilage, which is observed in particular in rheumatoid arthritis and in osteoarthritis.

In pathological situations, an irreversible degradation of articular cartilage takes place, as is the case in rheumatic diseases such as rheumatoid arthritis or osteoarthritis. In these pathologies, the cartilage degradation process predominates, leading to a destruction of the tissue and resulting in a loss of function.

25 At least twenty different matrix metalloproteases have been identified to date and are subdivided into four groups, the collagenases, the gelatinases, the stromelysins and the membrane-type MMPs (MT-MMPs), respectively.

Matrix metalloprotease-13 (MMP-13) is a collagenase-type MMP which constitutes the predominant collagenase observed during osteoarthritis, in the course of which pathology the chondrocyte directs the destruction of cartilage.

There is a need in the prior art for novel MMP inhibitors, more particularly for  
5 MMP-13 inhibitors, in order to prevent and/or correct the imbalance in the renewal of extracellular matrix tissue, such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary diseases (COPD), age-related macular degeneration (ARMD) and cancer.

10 MMP-inhibitor compounds are known. Most of these MMP-inhibitors are not selective for a single MMP, such as those described by Montana and Baxter (2000) or by Clark et al. (2000).

There is also a need in the prior art for novel inhibitors that are active on matrix metalloprotease-13, in order to enrich the therapeutic arsenal that can be used for treating  
15 pathologies associated with the destruction of the extracellular matrix and with cancer.

### **PRIOR ART DESCRIPTION**

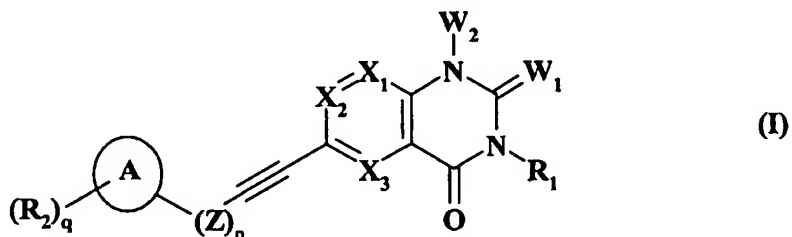
The patent application WO9826664 describes quinazolinone compounds which are used as new antifungic compounds. The US patent 5,389,631 describes new dioxoquinazoline and dioxobenzodiazepine amino acid derivatives which are analogs as  
20 fibrinogen receptor antagonists and can be used in the treatment of pathologies wherein inhibition of the fibrinogen of blood and inhibition of the aggregation of blood platelets are involved.

The compounds of the present application are novel and represent powerful inhibitors of MMP-13. They are consequently of use in the treatment of rheumatoid  
25 arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary diseases (COPDs), age-related degeneration (ARMD) and cancer.

**SUMMARY OF THE INVENTION**

The applicant has identified novel alkynylated fused ring pyrimidine compounds that are matrix metalloprotease inhibitors, and more specifically compounds that are selective MMP-13 inhibitors.

5 More specifically, the present invention relates to compounds of formula (I) :



wherein

**W<sub>1</sub>** represents an oxygen atom, a sulfur atom, or a -NR<sub>3</sub> group in which R<sub>3</sub> represents hydrogen atom, (C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxyl or cyano,

10 **W<sub>2</sub>** represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono(C<sub>1</sub>-C<sub>10</sub>)alkylamino, di(C<sub>1</sub>-C<sub>10</sub>)alkylamino, each alkyl moiety being identical or different,
- (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)alkenyl, (C<sub>3</sub>-C<sub>6</sub>)alkynyl, (C<sub>5</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl(C<sub>1</sub>-C<sub>10</sub>)alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected from halogen, amino, mono(C<sub>1</sub>-C<sub>10</sub>)alkylamino, di(C<sub>1</sub>-C<sub>10</sub>)alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)acyl, -C(=O)OR<sub>4</sub>, -OR<sub>4</sub> and -SR<sub>4</sub>, R<sub>4</sub> representing a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

or **W<sub>1</sub>** and **W<sub>2</sub>** form together a group of formula N-X<sub>4</sub>=W<sub>3</sub> (in which the nitrogen atom is bonded on the place of the group W<sub>1</sub> and the group W<sub>3</sub> is bonded on the place of the group W<sub>2</sub>) wherein:

- $W_3$  represents a nitrogen atom or a group  $-CR_5$  in which  $R_5$  is selected from :
    - a hydrogen atom,
    - $-OR_6$ ,  $-SR_6$  in which  $R_6$  is selected from hydrogen,  $(C_1-C_6)$ alkyl and  $(C_5-C_{10})$ aryl $(C_1-C_{10})$ alkyl;
    - 5    -  $(C_1-C_6)$ alkyl,  $(C_3-C_8)$ cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen,  $(C_5-C_{10})$ aryl,  $(C_5-C_{10})$ heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and  $(C_5-C_{10})$ aryl $(C_1-C_{10})$ alkyl, these groups being optionally substituted by
    - 10     $-(CH_2)_p-OH$  or  $-(CH_2)_p-NH_2$ , wherein  $p$  is an integer from 0 to 4 inclusive,
  - $X_4$  represents a nitrogen atom or a group  $-CR_7$  in which  $R_7$  is selected from hydrogen,  $-NR_8R_9$ ,  $-OR_8$ ,  $-SR_8$ ,  $(C_1-C_6)$ alkyl,  $(C_3-C_8)$ cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen,  $(C_5-C_{10})$ aryl,  $(C_5-C_{10})$ heteroaryl
  - 15    comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and  $(C_5-C_{10})$ aryl $(C_1-C_{10})$ alkyl, these groups being optionally substituted by  $-(CH_2)_p-OH$  or  $-(CH_2)_p-NH_2$ , wherein  $p$  is an integer from 0 to 4 inclusive, and in which  $R_8$  and  $R_9$ , identical or different, are selected from hydrogen,  $(C_1-C_6)$ alkyl and  $(C_5-C_{10})$ aryl $(C_1-C_{10})$ alkyl,
- 20     $X_1$ ,  $X_2$  and  $X_3$  represent, independently of each other, a nitrogen atom or a carbon atom, the said carbon atom being unsubstituted or substituted with a group selected from :
- $(C_1-C_6)$ alkyl, hydroxyl,  $(C_1-C_6)$ alkoxy, halogen, trifluoromethyl, cyano, nitro,
  - $-S(O)_{n_1}R_4$  wherein  $n_1$  represents an integer from 0 to 2 inclusive and  $R_4$  represents an hydrogen atom or a  $(C_1-C_6)$ alkyl group,
  - 25    • and  $-NR_{10}R_{11}$  wherein  $R_{10}$  and  $R_{11}$ , which may be identical or different, represent a group selected from hydrogen atom,  $(C_1-C_6)$ alkyl, and  $(C_5-C_{10})$ aryl $(C_1-C_{10})$ alkyl, or  $R_{10}$  and  $R_{11}$  form together with the nitrogen atom to which there are bonded, a 5- or 6-ring members which can optionally contain a second hetero atom selected from nitrogen and oxygen,
- 30    with the proviso that not more than two of the groups  $X_1$ ,  $X_2$  and  $X_3$  simultaneously represent a nitrogen atom,

**n** is an integer from 0 to 8 inclusive,

**Z** represents  $-\text{CR}_{12}\text{R}_{13}$ , wherein  $\text{R}_{12}$  and  $\text{R}_{13}$  independently of each other, represent a group selected from hydrogen,  $(\text{C}_1\text{-C}_6)\text{alkyl}$ , trihalogeno $(\text{C}_1\text{-C}_6)\text{alkyl}$ , halogen, amino, mono $(\text{C}_1\text{-C}_6)\text{alkylamino}$ , di $(\text{C}_1\text{-C}_6)\text{alkylamino}$  in which each alkyl moiety is identical or different,  $-\text{OR}_4$ ,  $-\text{SR}_4$ , and  $-\text{C}(=\text{O})\text{OR}_4$ ,  $\text{R}_4$  being as defined hereinbefore, or  $-\text{CR}_{12}\text{R}_{13}$  form together a carbonyl group, and

-when **n** is greater than or equal to 2, the hydrocarbon chain **Z** optionally contains one or more multiple bonds,

-and/or one of the carbon atoms in the hydrocarbon chain **Z** may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted or substituted with a  $(\text{C}_1\text{-C}_6)\text{alkyl}$ ,

**A** represents the residue of an aromatic or non-aromatic 5- or 6-membered monocycle comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, or a bicycle composed of two aromatic or non-aromatic 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur,

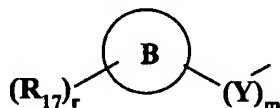
the groups **R<sub>2</sub>**, which may be identical or different, are selected from hydrogen,  $(\text{C}_1\text{-C}_6)\text{alkyl}$ , halogen, cyano, nitro, trihalogeno $(\text{C}_1\text{-C}_6)\text{alkyl}$ ,  $-\text{NR}_{10}\text{R}_{11}$ ,  $-\text{OR}_{14}$ ,  $-\text{SR}_{14}$ ,  $-\text{SOR}_{14}$ ,  $-\text{SO}_2\text{R}_{14}$ ,  $(\text{C}_1\text{-C}_6)\text{acyl}$ ,  $-(\text{CH}_2)_k\text{NR}_{10}\text{R}_{11}$ ,  $-\text{X}_5(\text{CH}_2)_k\text{NR}_{10}\text{R}_{11}$ ,  $(\text{CH}_2)_k\text{SO}_2\text{NR}_{14}\text{R}_{15}$ ,  $-\text{X}_5(\text{CH}_2)_k\text{C}(=\text{O})\text{OR}_{14}$ ,  $-(\text{CH}_2)_k\text{C}(=\text{O})\text{OR}_{14}$ ,  $-\text{X}_5(\text{CH}_2)_k\text{C}(=\text{O})\text{NR}_{14}\text{R}_{15}$ ,  $-(\text{CH}_2)_k\text{C}(=\text{O})\text{NR}_{14}\text{R}_{15}$  and  $-\text{X}_6\text{-R}_{16}$  in which :

- $\text{X}_5$  represents an oxygen atom, a sulfur atom, a  $-\text{NH}$  group, or a  $-\text{N}(\text{C}_1\text{-C}_6)\text{alkyl}$  group,
- **k** is an integer from 0 and 3 inclusive,
- $\text{R}_{10}$  and  $\text{R}_{11}$  are as defined hereinbefore,
- $\text{R}_{14}$  and  $\text{R}_{15}$ , identical or different, represent hydrogen or  $(\text{C}_1\text{-C}_6)\text{alkyl}$ ,
- $\text{X}_6$  represents a single bond,  $-\text{CH}_2-$ , an oxygen atom or a sulfur atom which is unsubstituted or substituted with one or two oxygen atoms,

- $R_{16}$  represents the residue of an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen, trihalogeno $(C_1-C_6)$ alkyl, hydroxyl,  $(C_1-C_6)$ alkoxy, mercapto,  $(C_1-C_6)$ alkylthio, amino, mono $(C_1-C_6)$ alkylamino, di $(C_1-C_6)$ alkylamino each alkyl moiety being identical or different, and when the ring is heterocyclic, it comprises from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur,

$q$  is an integer from 0 to 7 inclusive,

$R_1$  represents a group selected from hydrogen,  $(C_1-C_6)$ alkyl,  $(C_3-C_6)$ alkenyl, and  $(C_3-C_6)$ alkynyl, the groups alkyl, alkenyl and alkynyl being optionally substituted with one or more groups, which may be identical or different, selected from amino, mono $(C_1-C_6)$ alkylamino, di $(C_1-C_6)$ alkylamino in which each alkyl moiety is identical or different,  $(C_1-C_6)$ alkyl, cyano, trihalogeno $(C_1-C_6)$ alkyl,  $-C(=O)OR_4$ ,  $-OR_4$ ,  $-SR_4$ , in which  $R_4$  is as defined above, and the group of formula :



in which:

- $m$  is an integer from 0 to 8 inclusive,
- $Y$  represents  $-CR_{18}R_{19}$ , wherein  $R_{18}$  and  $R_{19}$  independently of each other, represent a group selected from hydrogen,  $(C_1-C_6)$ alkyl, phenyl, trihalogeno $(C_1-C_6)$ alkyl, halogen, amino, mono $(C_1-C_6)$ alkylamino, di $(C_1-C_6)$ alkylamino in which each alkyl moiety is identical or different,  $-OR_4$ ,  $-SR_4$  or  $-C(=O)OR_4$  wherein  $R_4$  is as defined above, and
  - when  $m$  is greater than or equal to 2, the hydrocarbon chain  $Y$  optionally contains one or more multiple bonds,
  - and/or one of the carbon atoms in the hydrocarbon chain  $Y$  may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted or substituted with  $(C_1-C_6)$ alkyl,
- $B$  represents a group selected from the residue of an aromatic or non-aromatic, 5- or 6-membered monocycle comprising from 0 to 4 hetero atoms selected from nitrogen,

oxygen and sulfur, and a bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur,

- r is an integer from 0 to 7 inclusive,
- 5 • the group(s) R<sub>17</sub> which may be identical or different are selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, cyano, nitro, trihalogeno(C<sub>1</sub>-C<sub>6</sub>)alkyl, -NR<sub>10</sub>R<sub>11</sub>, -OR<sub>14</sub>, -SR<sub>14</sub>, -SOR<sub>14</sub>, -SO<sub>2</sub>R<sub>14</sub>, (C<sub>1</sub>-C<sub>6</sub>)acyl, -(CH<sub>2</sub>)<sub>k</sub>NR<sub>10</sub>R<sub>11</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>NR<sub>10</sub>R<sub>11</sub>, -(CH<sub>2</sub>)<sub>k</sub>SO<sub>2</sub>NR<sub>14</sub>R<sub>15</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>14</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>14</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>14</sub>R<sub>15</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>14</sub>R<sub>15</sub> and the group of formula -X<sub>6</sub>-R<sub>16</sub> in
- 10 which X<sub>5</sub>, k, R<sub>10</sub>, R<sub>11</sub>, R<sub>14</sub>, R<sub>15</sub>, X<sub>6</sub> and R<sub>16</sub> are as defined hereinbefore, and

optionally, their optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

According to a first embodiment, the invention relates to compounds of formula (I) wherein :

- 15 W<sub>1</sub> represents an oxygen atom, a sulfur atom, or a -NR<sub>3</sub> group in which R<sub>3</sub> represents hydrogen atom, (C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxyl or cyano,

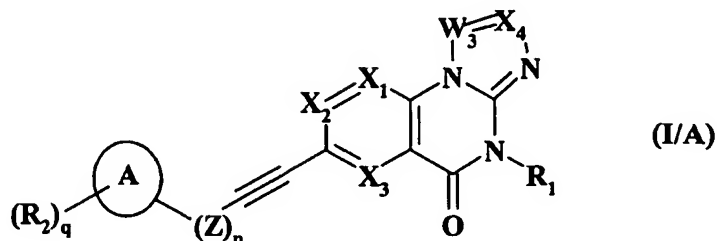
W<sub>2</sub> represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono(C<sub>1</sub>-C<sub>10</sub>)alkylamino, di(C<sub>1</sub>-C<sub>10</sub>)alkylamino, each alkyl moiety being identical or different,
- 20 • (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)alkenyl, (C<sub>3</sub>-C<sub>6</sub>)alkynyl, (C<sub>5</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl(C<sub>1</sub>-C<sub>10</sub>)alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected
- 25 from halogen, amino, mono(C<sub>1</sub>-C<sub>10</sub>)alkylamino, di(C<sub>1</sub>-C<sub>10</sub>)alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)acyl, -C(=O)OR<sub>4</sub>, -OR<sub>4</sub> and -SR<sub>4</sub>, R<sub>4</sub> representing a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

and X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, R<sub>1</sub>, R<sub>2</sub>, A, Z, n and q are as defined hereinbefore.



According to a second embodiment, the invention relates to compounds of formula (I) corresponding to formula (IA) :



wherein :

5 **W<sub>3</sub>** represents a nitrogen atom or a group -CR<sub>5</sub> in which R<sub>5</sub> is selected from :

- a hydrogen atom,
- -OR<sub>6</sub>, -SR<sub>6</sub> in which R<sub>6</sub> is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl;
- (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C<sub>5</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>10</sub>)heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl, these groups being optionally substituted by -(CH<sub>2</sub>)<sub>p</sub>-OH or -(CH<sub>2</sub>)<sub>p</sub>-NH<sub>2</sub>, wherein p is an integer from 0 to 4 inclusive,

15 **X<sub>4</sub>** represents a nitrogen atom or a group -CR<sub>7</sub> in which R<sub>7</sub> is selected from hydrogen, -NR<sub>8</sub>R<sub>9</sub>, -OR<sub>8</sub>, -SR<sub>8</sub>, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C<sub>5</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>10</sub>)heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl, these groups being optionally substituted by -(CH<sub>2</sub>)<sub>p</sub>-OH or -(CH<sub>2</sub>)<sub>p</sub>-NH<sub>2</sub>, wherein p is an integer from 0 to 4 inclusive,

and in which R<sub>8</sub> and R<sub>9</sub>, identical or different, are selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl,

and X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, R<sub>1</sub>, R<sub>2</sub>, A, Z, n and q are as defined in formula (I).

25 The invention relates particularly to the compounds of formula (I) in which:

**W<sub>2</sub>** represents a group selected from hydrogen atom, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>8</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl,

**W<sub>1</sub>** represents an oxygen atom or a sulfur atom,

**X<sub>1</sub>** represents a -CH group,

5      **X<sub>2</sub> represents a -CH group or a nitrogen atom,**

**X<sub>3</sub>** represents a -CH group,

and  $R_1, R_2, A, Z, n$  and  $q$  are as defined in formula (I).

The invention also relates to the compounds of general formula (I) in which:

W<sub>2</sub> represents a group selected from hydrogen atom, amino, mono(C<sub>1</sub>-C<sub>10</sub>)alkylamino, di(C<sub>1</sub>-C<sub>10</sub>)alkylamino each alkyl moiety being identical or different, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)alkenyl, (C<sub>3</sub>-C<sub>6</sub>)alkynyl, (C<sub>5</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, and (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl,

**W<sub>1</sub>** represents an oxygen atom or a sulfur atom,

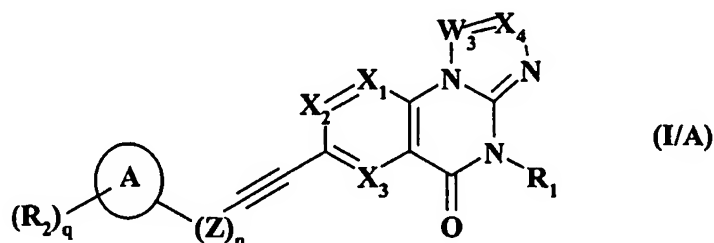
**X<sub>1</sub> represents a nitrogen atom or a -CH group**

15  $X_2$  represents a -CH group,

**X<sub>3</sub>** represents a -CH group,

and  $R_1, R_2, A, Z, n$  and  $q$  are as defined in formula (I).

The invention relates particularly to the compounds of formula (IA) :



20        wherein :

**W<sub>3</sub> represents -CR<sub>5</sub> wherein R<sub>5</sub> represents a hydrogen atom or a methyl group,**

**X<sub>4</sub>** represents a nitrogen atom or -CR<sub>7</sub>, wherein R<sub>7</sub> represents a hydrogen atom or a methyl group,

**$n$  is an integer from 1 to 4 inclusive,**

25 and  $X_1, X_2, X_3, R_1, R_2, A, Z$  and  $q$  are as defined in the formula (I).

The invention also relates to the compounds of formula (I) in which:

A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzo-1,2,5-thiadiazolyl, benzo-1,2,5-oxadiazolyl and indolyl,

5 q is an integer from 0 to 4 inclusive,

the group(s)  $R_2$ , which may be identical or different, are selected from hydrogen,  $(C_1-C_6)$ alkyl, halogen, cyano, nitro, trihalogeno $(C_1-C_6)$ alkyl,  $-NR_{14}R_{15}$ ,  $-OR_{14}$ ,  $-SO_2R_{14}$ ,  $-(CH_2)_kSO_2NR_{14}R_{15}$ ,  $-X_5(CH_2)_kC(=O)OR_{14}$ ,  $-(CH_2)_kC(=O)OR_{14}$ ,  $-X_5(CH_2)_kC(=O)NR_{14}R_{15}$ ,  $-(CH_2)_kC(=O)NR_{14}R_{15}$  and  $-X_6-R_{16}$  in which :

- 10
- $X_5$  represents an oxygen atom, a sulfur atom, or a -NH group,
  - k is an integer from 0 and 3 inclusive,
  - $R_{14}$  and  $R_{15}$  identical or different represent hydrogen or  $(C_1-C_6)$ alkyl,
  - $X_6$  represents an oxygen atom,
  - $R_{16}$  represents a phenyl group which is unsubstituted or substituted with one or more
- 15 groups, which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen, and hydroxyl,

and  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$ ,  $R_1$ , Z and n are as defined in formula (I).

The invention also relates to the compounds of formula (I) in which:

20 A represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, and benzodioxolyl,

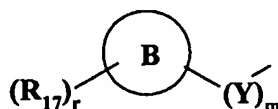
q is an integer from 0 to 4 inclusive,

the group(s)  $R_2$ , which may be identical or different, are selected from hydrogen,  $(C_1-C_6)$ alkyl, halogen, cyano, nitro, trihalogeno $(C_1-C_6)$ alkyl,  $-NR_{14}R_{15}$ ,  $-OR_{14}$ ,  $-SO_2R_{14}$ ,  $-(CH_2)_kSO_2NR_{14}R_{15}$ ,  $-X_5(CH_2)_kC(=O)OR_{14}$ ,  $-(CH_2)_kC(=O)OR_{14}$ ,  $-X_5(CH_2)_kC(=O)NR_{14}R_{15}$ , and  $-(CH_2)_kC(=O)NR_{14}R_{15}$  in which :

- 25
- $X_5$  represents an oxygen atom, a sulfur atom, or a -NH group,
  - k is an integer from 0 and 3 inclusive,

•  $R_{14}$  and  $R_{15}$  identical or different represent hydrogen or  $(C_1-C_6)$ alkyl,  
and  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$ ,  $R_1$ ,  $Z$  and  $n$  are as defined in formula (I).

The invention also relates to the compounds of formula (I) in which  $R_1$  represents hydrogen,  $(C_1-C_6)$ alkyl or the group of formula :

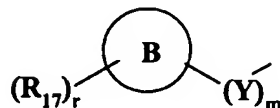


in which:

- $m$  is an integer from 0 to 3 inclusive,
- $Y$  represents  $-CR_{18}R_{19}$ , wherein  $R_{18}$  and  $R_{19}$  independently of each other, represent a group selected from hydrogen,  $(C_1-C_6)$ alkyl, and phenyl,
  - and when  $m$  is greater than or equal to 2, the hydrocarbon chain  $Y$  optionally contains one multiple bonds,
  - and/or one of the carbon atoms in the hydrocarbon chain  $Y$  may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted,
- $B$  represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzo-1,2,5-thiadiazolyl, benzo-1,2,5-oxadiazolyl, naphthyl and indolyl,
- $r$  is an integer from 0 to 3 inclusive,
- the group(s)  $R_{17}$  which may be identical or different are selected from hydrogen,  $(C_1-C_6)$ alkyl, halogen, cyano, nitro, trihalogeno $(C_1-C_6)$ alkyl,  $-NR_{14}R_{15}$ ,  $-OR_{14}$ ,  $-SO_2R_{14}$ ,  $(CH_2)_kSO_2NR_{14}R_{15}$ ,  $X_5(CH_2)_kC(=O)OR_{14}$ ,  $(CH_2)_kC(=O)OR_{14}$ ,  $X_5(CH_2)_kC(=O)NR_{14}R_{15}$ ,  $-(CH_2)_kC(=O)NR_{14}R_{15}$  wherein :
  - $k$  is an integer from 0 to 3 inclusive,
  - $X_5$  represents an oxygen atom, a sulfur atom, or a group  $-NH$ ,
  - $R_{14}$  and  $R_{15}$ , identical or different, represent a hydrogen atom or a  $(C_1-C_6)$ alkyl group,

and  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$ ,  $R_2$ ,  $Z$ ,  $n$  and  $q$  are as defined in formula (I).

The invention relates also to the compound of formula (I) in which  $R_1$  represents a group of formula :



in which:

- 5     •  $m$  is an integer from 0 to 3 inclusive,
- $Y$  represents  $-\text{CR}_{18}\text{R}_{19}$ , wherein  $R_{18}$  and  $R_{19}$  independently of each other, represent a group selected from hydrogen and methyl,
  - and when  $m$  is greater than or equal to 2, the hydrocarbon chain  $Y$  optionally contains one double bonds,
  - 10   – and/or one of the carbon atoms in the hydrocarbon chain  $Y$  may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted,
- $B$  represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, and benzodioxolyl,
- 15     •  $r$  is an integer from 0 to 3 inclusive,
- the group(s)  $R_{17}$  which may be identical or different are selected from hydrogen,  $(\text{C}_1\text{-C}_6)\text{alkyl}$ , halogen, cyano, nitro, trihalogeno $(\text{C}_1\text{-C}_6)\text{alkyl}$ ,  $-\text{NR}_{14}\text{R}_{15}$ ,  $-\text{OR}_{14}$ ,  $-\text{SO}_2\text{R}_{14}$ ,  $(\text{CH}_2)_k\text{SO}_2\text{NR}_{14}\text{R}_{15}$ ,  $\text{X}_5(\text{CH}_2)_k\text{C}(=\text{O})\text{OR}_{14}$ ,  $(\text{CH}_2)_k\text{C}(=\text{O})\text{OR}_{14}$ ,  $\text{X}_5(\text{CH}_2)_k\text{C}(=\text{O})\text{NR}_{14}\text{R}_{15}$ ,  $-(\text{CH}_2)_k\text{C}(=\text{O})\text{NR}_{14}\text{R}_{15}$  wherein :
  - 20   –  $k$  is an integer from 0 to 3 inclusive,
  - $\text{X}_5$  represents an oxygen atom, a sulfur atom, or a group  $-\text{NH}$ ,
  - $\text{R}_{14}$  and  $\text{R}_{15}$ , identical or different, represent a hydrogen atom or a  $(\text{C}_1\text{-C}_6)\text{alkyl}$  group,

and  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$ ,  $R_2$ ,  $Z$ ,  $n$  and  $q$  are as defined in formula (I).

- 25   Preferred compounds of the invention are those compounds of formula (I) wherein  $n$  is equal to one.

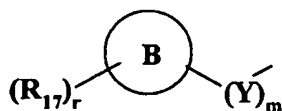
Advantageously, preferred compounds of the invention are those compounds of formula (I) wherein Z represents a group  $-CR_{12}R_{13}$  in which  $R_{12}$  and  $R_{13}$  represent each a hydrogen atom.

Another preferred compounds of the invention are compounds of formula (I) wherein A represents a 5- to 6- membered aromatic monocycle optionally substituted by one or more groups  $R_2$  as defined in the compound of formula (I).

The substituent A that is preferred according to the invention is the phenyl group optionally substituted by one group  $R_2$  as defined in the compound of the formula (I).

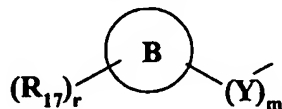
Especially preferred compounds of the invention are compounds of formula (I) wherein A represents a phenyl group and  $R_2$  represents a methoxy group.

Still other preferred compounds of the invention are compounds of formula (I) wherein  $W_2$  represents an oxygen atom,  $W_1$  represents a linear or branched  $(C_1-C_6)$ alkyl group and  $R_1$  represents a group of formula :



in which Y, B,  $R_{17}$ , m and r are as defined in the compound of formula (I).

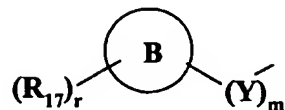
The substituent  $R_1$  that is preferred according to the invention is the group of formula :



in which m is equal to one, Y represents a methylene group, B represents a phenyl group which is optionally substituted with one group  $R_{17}$  which represents a group  $(CH_2)_k-C(=O)OR_{14}$  in which k and  $R_{14}$  are as defined in the compound of formula (I).

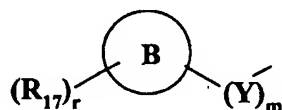
Still other preferred compounds of the invention are compounds of formula (IA) wherein  $W_1$  and  $W_2$  form together a group or formula  $N-X_4=W_3$  wherein  $W_3$  represents a group -

CR<sub>5</sub> in which R<sub>5</sub> is an hydrogen atom, X<sub>4</sub> represents an nitrogen atom and R<sub>1</sub> represents a group of formula :



in which Y, B, R<sub>17</sub>, m and r are as defined in the compound of formula (IA).

- 5 Still other preferred compounds of the invention are compounds of formula (IA) wherein R<sub>1</sub> represents a group of formula :



- in which m is equal to one, Y represents a methylene group, B represents a phenyl group which is optionally substituted with one group R<sub>17</sub> which represents a group  
 10 -(CH<sub>2</sub>)<sub>k</sub>-C(=O)OR<sub>14</sub> in which k and R<sub>14</sub> are as defined in the compound of formula (IA).

More particularly, the invention related to the following compounds of formula (I) :

- Methyl 4-{6-[3-(4-methoxyphenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate,  
 4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-  
 15 benzoic acid,  
 4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid,  
 4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid,  
 20 4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl}-benzoic acid,  
 4-Benzyl-7-(3-phenyl-prop-1-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one,  
 4-Benzyl-7-[(4-methoxyphenyl)-prop-1-ynyl]-4H-[1,2,4]-triazolo[4,3-a]quinazolin-5-one,  
 Methyl 4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5H-[1,2,4]triazolo[4,3-a]  
 25 quinazolin-4-ylmethyl}-benzoate,  
 4-[5-Oxo-7-(3-phenyl-prop-1-ynyl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl]-benzoic acid,

and 4-(1-Methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid.

The optical isomers, the N-oxides, as well as the addition salts with a pharmaceutically-acceptable acid or base, of the preferred compounds form an integral part of the invention.

- 5 The invention also relates to a pharmaceutical composition comprising as active ingredient an effective amount of a compound of formula (I) together with one or more pharmaceutically-acceptable excipients or carriers.

Another embodiment of the invention concerns the use of the compound of formula (I) for the preparation of a medicinal product intended for treating a disease involving therapy by  
10 inhibition of matrix metalloprotease, and more particularly of type-13 matrix metalloprotease.

The invention also relates to a method for treating a living body afflicted with a disease involving a therapy by inhibition of matrix metalloprotease, and more particularly of type-13 matrix metalloprotease, the said method comprising the administration of an effective  
15 amount of a compound of formula (I) to a patient in need thereof.

A preferred method of treatment according to this invention is treatment of a disease selected from arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary diseases, age-related degeneration  
20 and cancers.

### **DETAILED DESCRIPTION OF THE INVENTION**

The compounds provided by this invention are those defined in formula (I). In formula (I), it is understood that :

- 25 - a (C<sub>1</sub>-C<sub>6</sub>)alkyl group and a (C<sub>1</sub>-C<sub>10</sub>)alkyl group denote a linear or branched group containing respectively from 1 to 6 or from 1 to 10 carbon atoms ; example of such groups,



without implying any limitation are methyl, ethyl, propyl, isopropyl, tert-butyl, neopentyl, hexyl, heptyl, 3-methyl-hexyl, ...

- a (C<sub>3</sub>-C<sub>6</sub>)alkenyl group denotes a linear or branched group containing from 3 to 6 carbon atoms, and one or more double bonds ; examples of such groups without implying any limitation are allyl, 3-buten-1-yl, 2-methyl-buten-1-yl, hexenyl, ...

- a (C<sub>3</sub>-C<sub>6</sub>)alkynyl group denotes a linear or branched group containing from 3 to 6 carbon atoms, and one or more triple bonds ; examples of such groups without implying any limitation are 3-butyn-1-yl, 2-methyl-butyn-1-yl, hexynyl, ...

- a (C<sub>1</sub>-C<sub>6</sub>)alkoxy group means the alkyl group as mentioned above bound through an oxygen atom ; examples of such compounds without implying any limitation are methoxy, ethoxy, *n*-propyloxy, *tert*-butyloxy, ....

- a (C<sub>1</sub>-C<sub>6</sub>)alkylamino or (C<sub>1</sub>-C<sub>10</sub>)alkylamino means the alkyl groups as defined above bound through a nitrogen atom ; example of such groups, without implying any limitation are methyl amino, isobutyl amino, dimethylamino, ethylamino, diethylamino, ...

- a (C<sub>5</sub>-C<sub>10</sub>)aryl group denotes an aromatic system containing from 5 to 8 carbon atoms ; examples of such groups without implying any limitation are cyclopentadienyl, phenyl, naphthyl, indenyl,...

- a (C<sub>5</sub>-C<sub>10</sub>)heteroaryl group denotes an aromatic system as described above in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen ; examples of such groups without implying any limitation are furyl, thienyl, pyrrolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzofuryl, benzothieryl, indolyl, quinolyl, isoquinolyl, benzodioxolyl, benzodioxinyl, benzo[1,2,5]thiadiazolyl, benzo[1,2,5]oxadiazolyl,...

- a (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl group denotes a cyclic system containing from 3 to 10 carbon atoms ; examples of such groups without implying any limitation are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, cycloheptyl, adamantyl, decalanyl, norbornyl, ...

- a trihalogeno(C<sub>1</sub>-C<sub>6</sub>)alkyl group denotes an alkyl group as defined above which contains a trihalogeno group ; examples of such groups without implying any limitation are trifluoromethyl, 2,2,2-trifluoroethyl, ...

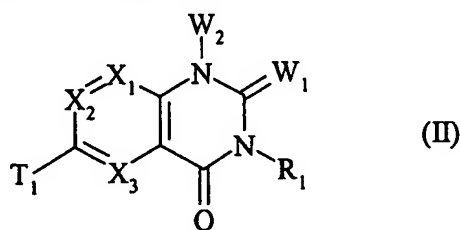
- a (C<sub>1</sub>-C<sub>6</sub>)acyl group denotes an alkyl group or a aryl group as defined above bound through a carbonyl group ; examples of such groups without implying any limitation are acetyl, ethylcarbonyl, benzoyl, ...
- a multiple bond denotes double bond or triple bond,
- 5      - optical isomers refer to racemates, enantiomers and diastereoisomers.

The invention also relates to the pharmaceutically acceptable salts of the compounds of formula (I). A review of the pharmaceutically acceptable salts will be found in *J. Pharm. Sci.*, 1977, 66, 1-19.

10 Pharmaceutically acceptable acids mean non-toxic mineral or organic acids. Among those there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphonic acid, nitric acid, citric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, ascorbic acid, oxalic acid, methanesulfonic acid, camphoric acid, benzoic acid, toluenesulfonic acid, etc...

15 Pharmaceutically acceptable bases mean non-toxic mineral or organic bases. Among those, there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, calcium hydroxide, triethylamine, tert-butylamine, dibenzylethylenediamine, piperidine, pyrrolidine, benzylamine, quaternary ammonium hydroxides etc...

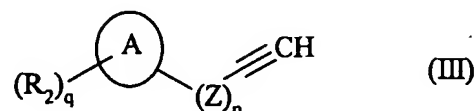
20 The invention also relates to a process for the preparation of compounds of formula (I), which uses as starting material a compound of formula (II):



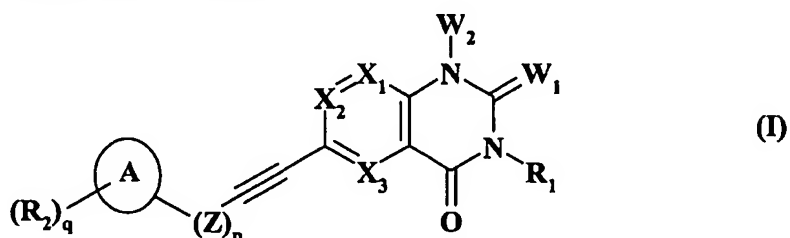
in which R<sub>1</sub>, W<sub>1</sub>, W<sub>2</sub>, X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> have the same definitions as the compounds of formula (I), and T<sub>1</sub> represents a group selected from hydrogen, halogen, mesylate, triflate, formyl, acetyl, and ester,

25 compound of formula (II) which is treated :

❖ either when  $T_1$  represents an halogen atom, a mesylate group, or a triflate group, in the presence of a base under conditions of palladium-catalyzed alkynylation with a compound of formula (III):

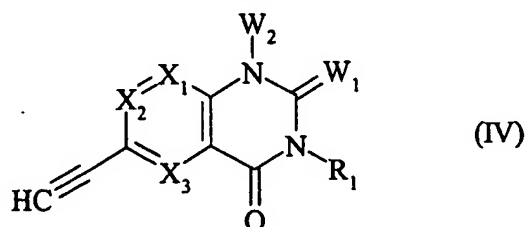


- 5 in which A, Z,  $R_2$ , q and n are as defined for the compounds of formula (I), to yield the compounds of formula (I),



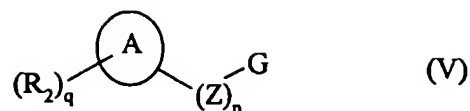
- ❖ or when  $T_1$  represents an hydrogen atom, with iodine to yield *in situ* the corresponding iodide intermediate, which is treated directly without isolation or purification, with a compound of formula (III) as described hereinbefore, under conditions of palladium-catalyzed alkynylation in the presence of a base,
- 10 to yield the compounds of formula (I),

- ❖ or when  $T_1$  represents an acetyl group, first with lithium diisopropylamine at  $-78^\circ\text{C}$  in an inert solvent to provide an enolate, second with diethyl chlorophosphate and subsequently with lithium diisopropylamine, to yield a compound of formula (IV):
- 15

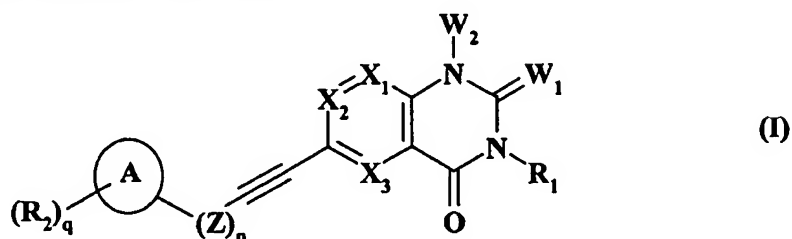


in which  $R_1$ ,  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$  and  $X_3$  are as defined hereinbefore, and condensing the compound of formula (IV), in the presence of triphenylphosphine and  $\text{PdCl}_2(\text{PPh}_3)_2$ , under basic conditions to a compound of formula (V):

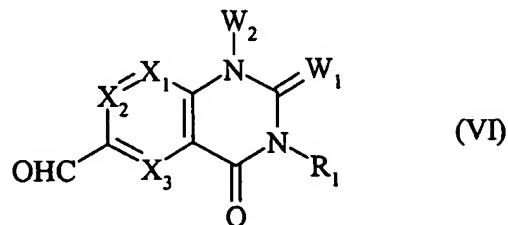
19



in which A, Z, R<sub>2</sub>, q and n are as defined hereinbefore and G represents a leaving group, to yield the compound of formula (I),



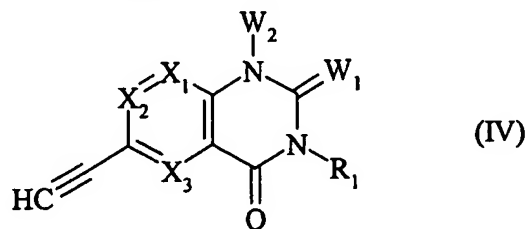
- 5      ❖ or when T<sub>1</sub> represents an ester group, with a reductive agent, to yield the corresponding aldehyde compound of formula (VI):



in which R<sub>1</sub>, W<sub>1</sub>, W<sub>2</sub>, X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are as defined hereinbefore,

and subsequently :

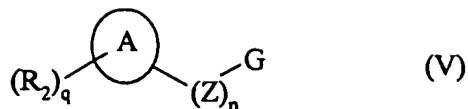
- 10      • either condensing said compound of formula (VI), in basic conditions, with diazomethyl trimethyl silane or with diazomethyl diethoxy phosphonate, to yield, after basic treatment, a compound of formula (IV) as defined hereinbefore :



and adding said compound of formula (IV) to a compound of formula (V) as described hereinbefore :

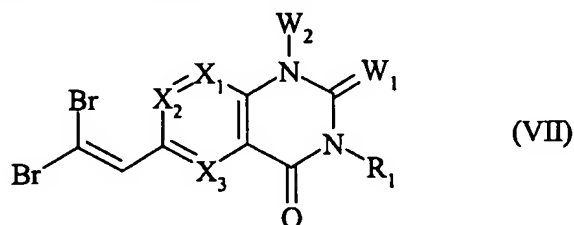
15

20

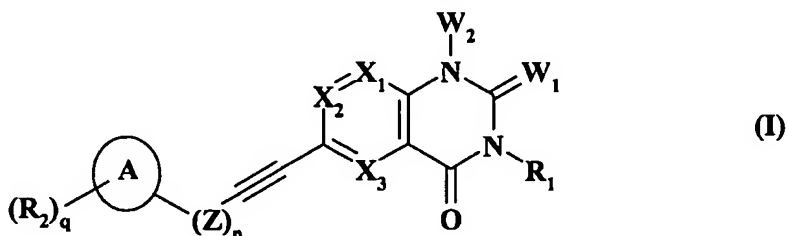


in which  $R_2$ , A, Z, q, n and G are as defined hereinbefore,  
to yield the compound of formula (I),

- or reacting, said compound of formula (VI), with tetrabromomethane in the presence  
of triphenylphosphine in an aprotic solvent to yield a compound of formula (VII) :



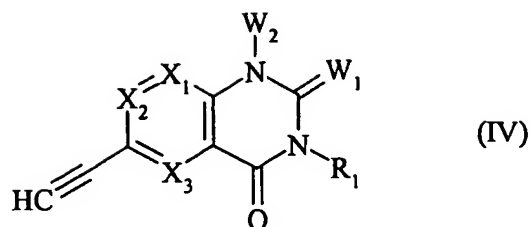
in which  $R_1$ ,  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$  and  $X_3$  are as defined hereinbefore,  
and dehalogenating said compound of formula (VII) through treatment with a strong  
base in an inert solvent, or with butyllithium in presence of triphenylphosphine and  
zinc, to yield the compound of formula (IV) as defined hereinbefore,  
and reacting said compound of formula (IV) with a compound of formula (V) as  
defined in the previous step to yield a compound of a general formula (I):



The compound of formula (I) are purified, where appropriate, according to a conventional  
purification technique, and separated, where appropriate, into their different isomers  
according to a conventional separation technique, and converted, where appropriate, into  
addition salts thereof with a pharmaceutically-acceptable acid or base.

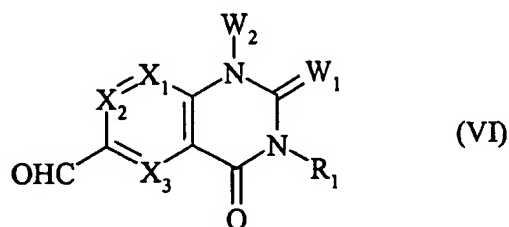
The compounds of formula (IV):

21



wherein  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$  and  $R_1$  are as defined in compounds of formula (I)  
are novel useful intermediates for the preparation of compounds of formula (I).

The compounds of formula (VI)

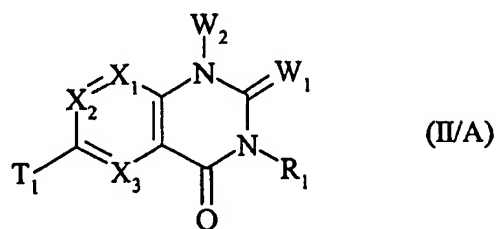


5

wherein  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$  and  $R_1$  are as defined in compounds of formula (I)  
are also novel useful intermediates for the preparation of compounds of formula (I).

The compounds of formula (II) used as starting material may be distinguished into two  
groups which are respectively represented :

10      ➤ by the compounds of the formula (II/A) :



wherein :

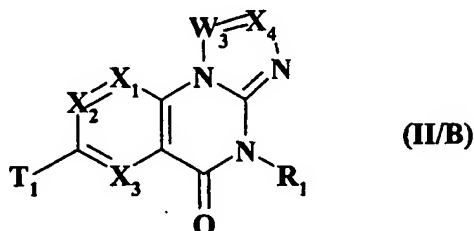
$W_1$  represents an oxygen atom, a sulfur atom, or a  $-NR_3$  group in which  $R_3$  represents  
hydrogen atom,  $(C_1-C_6)$ alkyl, hydroxyl or cyano,

15       $W_2$  represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono( $C_1-C_{10}$ )alkylamino,  
di( $C_1-C_{10}$ )alkylamino, each alkyl moiety being identical or different,

- (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)alkenyl, (C<sub>3</sub>-C<sub>6</sub>)alkynyl, (C<sub>5</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl(C<sub>1</sub>-C<sub>10</sub>)alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected from halogen, amino, mono(C<sub>1</sub>-C<sub>10</sub>)alkylamino, di(C<sub>1</sub>-C<sub>10</sub>)alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)acyl, -C(=O)OR<sub>4</sub>, -OR<sub>4</sub> and -SR<sub>4</sub>, R<sub>4</sub> representing a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- 10 T<sub>1</sub> represents a group selected from hydrogen, halogen, mesylate, triflate, formyl, acetyl, and ester, and R<sub>1</sub>, X<sub>1</sub>, X<sub>2</sub>, and X<sub>3</sub> are as defined in the compounds of formula (I),

➤ and by the compounds of formula (II/B) :



wherein :

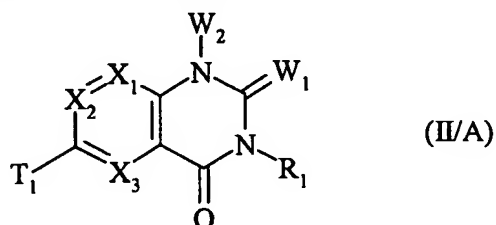
- 15 W<sub>3</sub> represents a nitrogen atom or a group -CR<sub>5</sub> in which R<sub>5</sub> is selected from :
- a hydrogen atom,
  - -OR<sub>6</sub>, -SR<sub>6</sub> in which R<sub>6</sub> is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>5</sub>-C<sub>8</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl;
  - (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C<sub>5</sub>-C<sub>8</sub>)aryl, (C<sub>5</sub>-C<sub>8</sub>)heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C<sub>5</sub>-C<sub>8</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl, these groups being optionally substituted by -(CH<sub>2</sub>)<sub>p</sub>-OH or -(CH<sub>2</sub>)<sub>p</sub>-NH<sub>2</sub>, wherein p is an integer from 0 to 4 inclusive,
- 20

- 5  $X_4$  represents a nitrogen atom or a group  $-CR_7$  in which  $R_7$  is selected from hydrogen,  $-NR_8R_9$ ,  $-OR_8$ ,  $-SR_8$ ,  $(C_1-C_6)$ alkyl,  $(C_3-C_{10})$ cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen,  $(C_5-C_{10})$ aryl,  $(C_5-C_{10})$ heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and  $(C_5-C_{10})$ aryl $(C_1-C_{10})$ alkyl, these groups being optionally substituted by  $-(CH_2)_p-OH$  or  $-(CH_2)_p-NH_2$  wherein  $p$  is an integer from 0 to 4 inclusive,
- and in which  $R_8$  and  $R_9$ , identical or different, are selected from hydrogen,  $(C_1-C_6)$ alkyl and  $(C_5-C_{10})$ aryl $(C_1-C_{10})$ alkyl,

- 10  $T_1$  represents a group selected from hydrogen, halogen, mesylate, triflate, formyl, acetyl, and ester, and  $R_1$ ,  $X_1$ ,  $X_2$ , and  $X_3$  are as defined in the compound of formula (I).

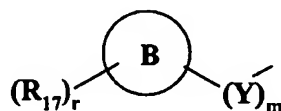
In an advantageous embodiment of the invention, the process for the preparation of compounds of formula (I) comprises the following step :

- reacting as starting material, a compound of formula (II/A) :



15

in which  $W_1$  represents an oxygen atom,  $W_2$  represents a  $(C_1-C_6)$ alkyl group,  $X_1$  represents a  $-CH$  group,  $X_2$  represents a nitrogen atom or a  $-CH$  group,  $X_3$  represents a  $-CH$  group, and  $T_1$  represent a iodine atom or a triflate group, and  $R_1$  represents a group of formula :



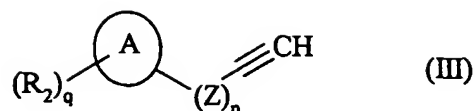
20

in which  $Y$  represents a methylene group,  $m$  is equal to one,  $B$  represents a phenyl group,  $R_{17}$  is as defined in the compound of formula (I) and  $r$  is equal to one,

- with, as reagent, a compound of formula (III) :

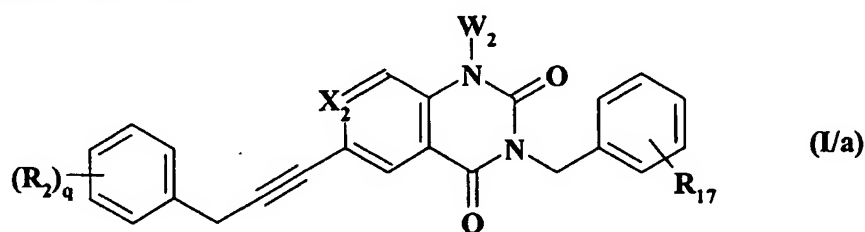


24



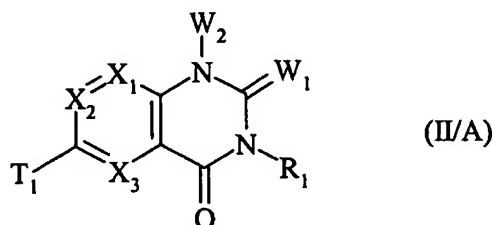
in which Z represents a methylene group, n is equal to one, A is a phenyl group, q is equal to zero or one, and R<sub>2</sub> is as defined in the compound of formula (I),

to yield a compound of formula (I/a), which constitutes a particular subgroup of the compounds of formula (I):



in which W<sub>2</sub>, X<sub>2</sub>, R<sub>2</sub>, q and R<sub>17</sub> are as defined hereinbefore.

The compounds of formula (II/A)



wherein :

W<sub>1</sub> represents an oxygen atom, a sulfur atom, or a -NR<sub>3</sub> group in which R<sub>3</sub> represents hydrogen atom, (C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxyl or cyano,

W<sub>2</sub> represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono(C<sub>1</sub>-C<sub>10</sub>)alkylamino, di(C<sub>1</sub>-C<sub>10</sub>)alkylamino, each alkyl moiety being identical or different,
- (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)alkenyl, (C<sub>3</sub>-C<sub>6</sub>)alkynyl, (C<sub>5</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl(C<sub>1</sub>-C<sub>10</sub>)alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected

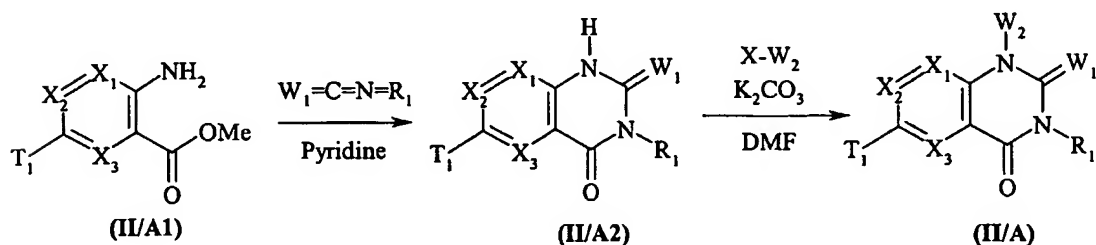
from halogen, amino, mono(C<sub>1</sub>-C<sub>10</sub>)alkylamino, di(C<sub>1</sub>-C<sub>10</sub>)alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)acyl, -C(=O)OR<sub>4</sub>, -OR<sub>4</sub> and -SR<sub>4</sub>, R<sub>4</sub> representing a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

- 5 T<sub>1</sub> represents a halogen atom,  
and R<sub>1</sub>, X<sub>1</sub>, X<sub>2</sub>, and X<sub>3</sub> are as defined in the compounds of formula (I),  
are also novel useful intermediates for the preparation of compounds of formula (I).

The compounds of formula (II/A) may be obtained through the synthetic way described in scheme 1.

10

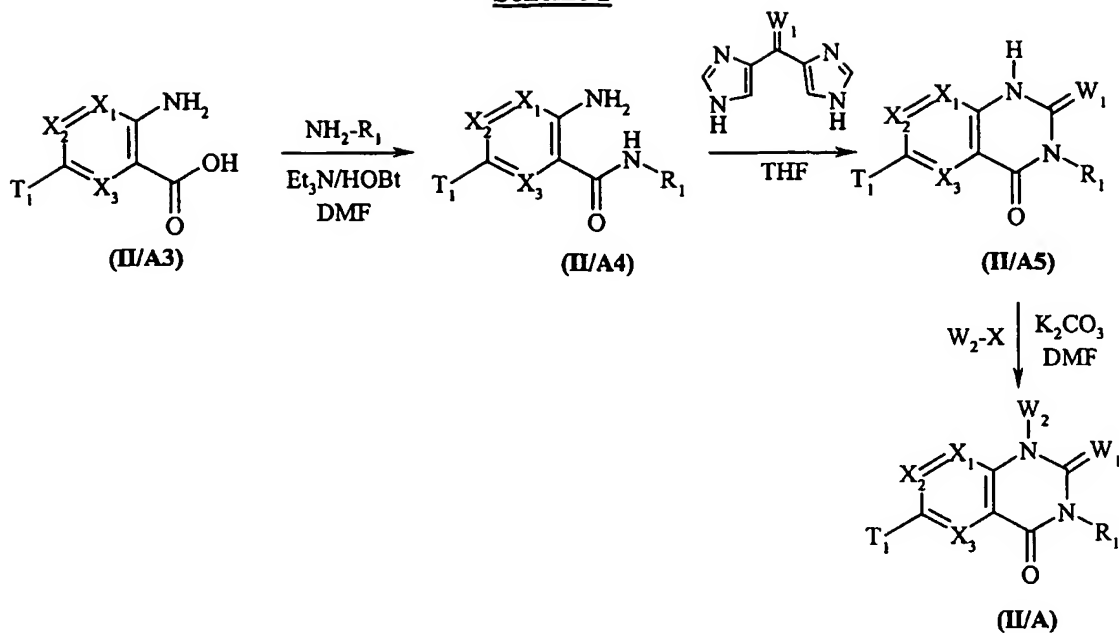
### Scheme 1



In these compounds of formulae (II/A1) and (II/A2), the substituents X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, W<sub>1</sub>, W<sub>2</sub>, R<sub>1</sub> and T<sub>1</sub> are as defined in the compounds of formula (II/A). In the compound X-W<sub>2</sub>, W<sub>2</sub> is as defined hereinbefore and X represents a leaving group.

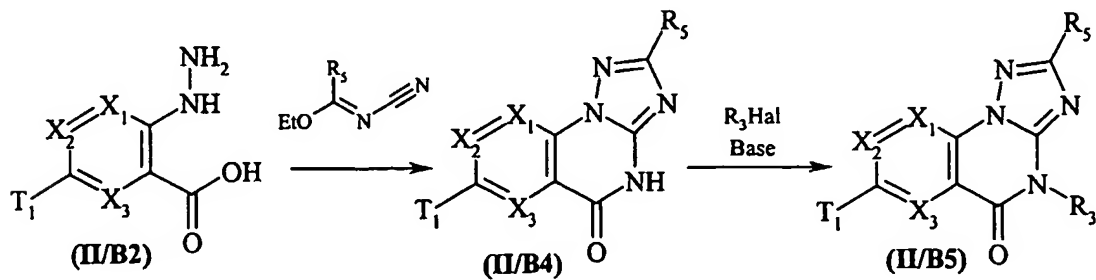
- 15 The starting material (II/A1) is either a commercial product or is obtained according to conventional methods of organic synthesis well known to the person skilled in the art.

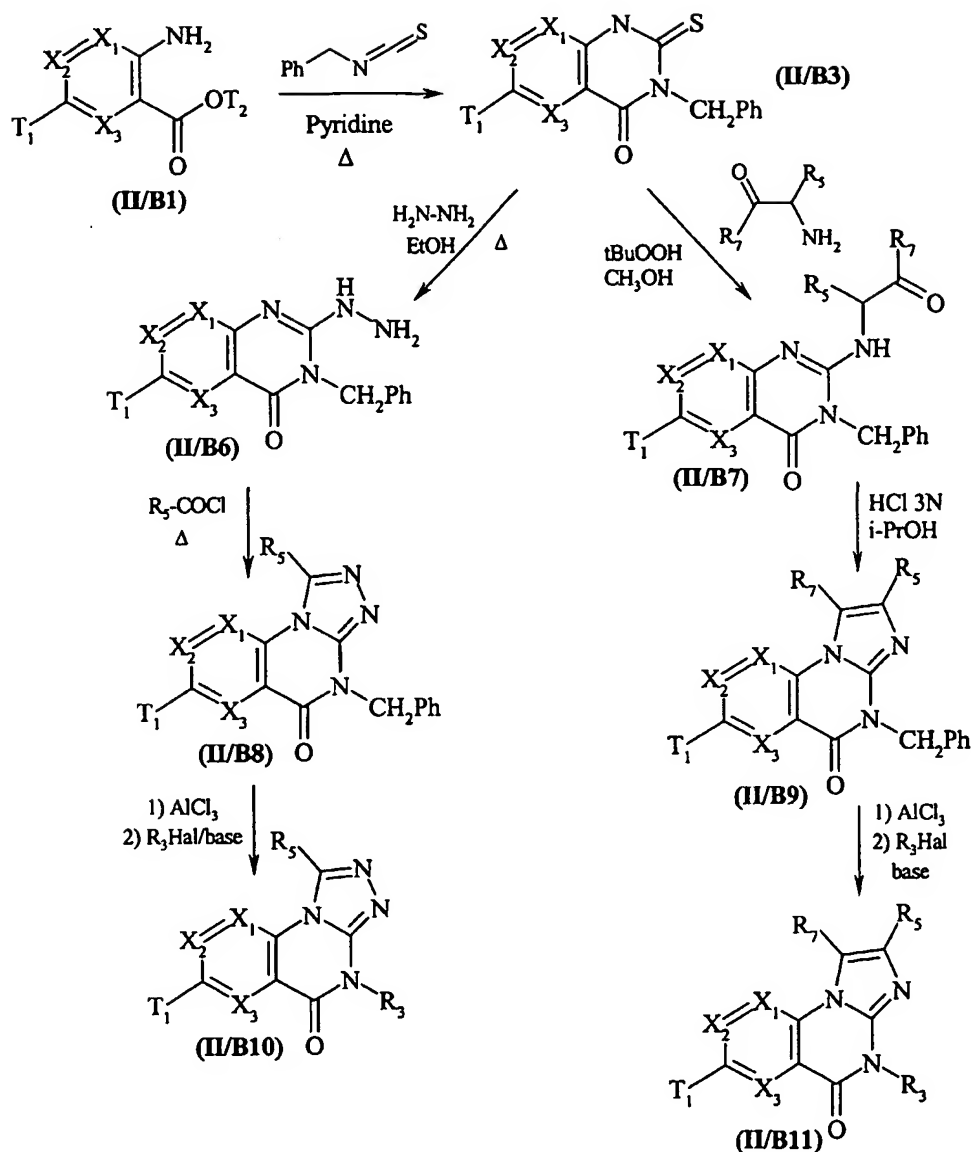
In another preferred embodiment, compounds of formula (II/A), where W<sub>1</sub> represents an oxygen atom or a sulfur atom, may be obtained through the synthetic way described in scheme 2.

**Scheme 2**

In a first step the acid function of compound (II/A3) is transformed into an amide group by reaction with a primary amine in usual conditions of organic chemistry to yield the compound (II/A4). This intermediate is then treated with 1,1'-carbonyldiimidazole or 1,1'-thiocarbonyldiimidazole, depending whether of  $W_1$  is an oxygen atom or a sulfur atom, in anhydrous tetrahydrofuran, to yield a compound of formula (II/A5), which is treated in the same conditions as those described in scheme 1 to obtain the compound of formula (II/A).

Compounds of the formula (II/B) are obtained through the synthetic way described in scheme 3 and in scheme 4.

**Scheme 3**

**Scheme 4**

In Scheme 3 the compound (II/B5) is obtained from substrate (II/B2) which is commercially available or obtained through usual methods of organic synthesis. The compound (II/B2) is treated with an alkyl *N*-cyanoimide to give a compound of formula (II/B4). The substitution of NH in position 4 with a halide in the presence of a base like cesium carbonate in an aprotic solvent leads to the formation of a compound of formula (II/B5) which represents a particular subgroup of compounds of formula (II) used as starting material in the general process for manufacturing compounds of formula (I).

In Scheme 4 the compound (II/B10) is obtained starting from compound (II/B1) which is treated in a first step with benzyl isothiocyanate to give the thiocarbonyl derivative (II/B3). This compound is heated, in a refluxing alcohol, in the presence of hydrazine hydrate to give the corresponding hydrazine (II/B6) which is in turn cyclized by reaction with an acid chloride or an orthoester to yield compound of formula (II/B8). This compound is then debenzylated by usual treatment and the N4-debenzylated atom is substituted by a halide in a basic medium, for example by addition of cesium carbonate in dimethylformamide to yield the product of formula (II/B10). The compound of formula (II/B10) is a particular subgroup of the compounds of formula (II) used as starting material in the general process for manufacturing compounds of formula (I).

In Scheme 4, the compound (II/B11) is obtained starting from compound (II/B1) which is transformed in a first step into a compound of formula (II/B3) as described hereinbefore. This compound (II/B3) is then treated in an alcoholic solvent such as methanol or ethanol, in the presence of a peroxide for initiating the oxidation of the starting thiol. The amino ketone (II/B6) obtained thereby is readily cyclized in the presence of acid, in an alcoholic solvent such as *isopropanol* to yield a compound of formula (II/B9) which is debenzylated and subsequently substituted on the N4 as described hereinbefore in order to obtain the product of formula (II/B11). The compound of formula (II/B11) is a particular subgroup of the compounds of formula (II) used as starting material in the general process for manufacturing compounds of formula (I).

Generally, isomers of the compounds of the invention are understood to be optical isomers such as enantiomers and diastereoisomers. More especially, pure enantiomeric forms of the compounds of the invention may be separated by starting from mixtures of enantiomers which are reacted with a racemate-separating agent that can be released, the said agent being itself in the form of a pure enantiomer, which allows the corresponding diastereoisomers to be obtained. The diastereoisomers are then separated according to the separation techniques well known to the person skilled in the art, such as crystallization or chromatography, and the separating agent is then removed using conventional techniques of organic synthesis, resulting in a pure enantiomer.

The compounds of the invention that are present in the form of a mixture of diastereoisomers are isolated in a pure form by using conventional separation techniques such as chromatography.

5 As mentioned above, compounds of formula (I) of the present invention are matrix metalloprotease inhibitors, and more particularly inhibitors of the enzyme MMP-13.

In this respect, their use is recommended for the treatment of diseases or complaints involving a therapy by MMP-13 inhibition. By way of example, the use of the compounds of the present invention may be recommended for the treatment of any pathology in which destruction of extracellular matrix tissue occurs, and most particularly pathologies such as  
10 arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease, age-related macular degeneration and cancers.

The present invention also relates to pharmaceutical compositions comprising as active  
15 ingredient at least one compound of formula (I), an isomer thereof, a N-oxide thereof, or an addition salt thereof with a pharmaceutically-acceptable acid or base, alone or in combination with one or more pharmaceutically-acceptable, inert, non-toxic excipients or carriers.

20 Among the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, intravaginal, rectal, nasal, perlingual, buccal, ocular or respiratory administration.

Pharmaceutical compositions according to the invention for parenteral injections especially include aqueous and non-aqueous sterile solutions, dispersions, suspension and emulsions,  
25 and also sterile powders for reconstituting injectable solutions or dispersions.

Pharmaceutical compositions according to the invention for oral administration in solid form especially include tablets or dragées, sublingual tablets, sachets, gelatin capsules and granules, for oral, nasal, buccal or ocular administration in liquid form, especially include emulsions, solutions, suspensions, drop, syrups and aerosols.

- 5      Pharmaceutical compositions for rectal or vaginal administration are preferably suppositories, and those for per- or trans-cutaneous administration especially include powders, aerosols, creams, ointment, gels and patches.

The pharmaceutical compositions mentioned hereinbefore illustrate the invention but do not limit it in any way.

- 10     Among the pharmaceutically acceptable, inert, non-toxic excipients or carriers there may be mentioned, by way of non-limiting example, diluents, solvents, preservatives, wetting agents, emulsifiers, dispersing agents, binders, swelling agents, disintegrating agents, retardants, lubricants, absorbents, suspending agents, colourants, aromatizing agents etc...

- 15     The useful dosage varies according to the age and weight of the patient, the administration route, the pharmaceutical composition used, the nature and severity of the disorder and the administration of any associated treatments. The dosage ranges from 2 mg to 1 g per day in one or more administrations. The compositions are prepared by methods that are common to those skilled in the art and generally comprise 0.5% to 60% by weight of active principle (compound of formula (I)) and 40% to 99.5% by weight of pharmaceutically  
20     acceptable excipients or carriers.

The examples that follow illustrate the invention but do not limit it in any way.

- 25     The starting materials used are products that are known or that are prepared according to known operating procedures. The various preparations yield synthetic intermediates that are useful in preparation of the compounds of the invention. Some of these intermediates are new compounds.

The structures of the compounds described in the Examples and Preparations were determined according to the usual spectrophotometric techniques (infrared, nuclear magnetic resonance, mass spectrometry, ...)

In the Preparations and Examples, it is understood that :

- 5       - DMF means Dimethylformamide,
- THF means Tetrahydrofurane,
- DMSO means Dimethylsulfoxide,
- TOTU means O-(ethoxycarbonyl)cyanomethylamino]-*N-N-N'-N'*-tetramethyl  
          uronium fluoroborate

## 10       **EXAMPLES**

### ***Preparation A : 4-(6-Iodo-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid***

#### **Step 1 : Methyl 4-[(2-amino-5-iodo-benzoylamino)-methyl]-benzoate**

To a stirred solution of 15 g (74.4 mmol) of methyl 4-(aminomethyl)benzoate hydrochloride, 300 ml of dimethylformamide and 10.3 ml (7.53g, 74.4 mmol) of triethylamine were added, at room temperature, followed by 10.06 g (74.4 mmol) of 1-hydroxybenzotriazole hydrate, 19.6 g (74.4 mmol) of 2-amino-5-iodobenzoic acid and 14.3 g (74.4 mmol) of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride. After stirring at room temperature overnight, the mixture was concentrated and the residue was dissolved in 300 ml of dichloromethane. The organic phase was washed with 150 ml H<sub>2</sub>O, 150 ml HCl 1N, and 150 ml H<sub>2</sub>O, dried over sodium sulfate and concentrated. The residue was recrystallized from 170 ml acetonitrile to afford after filtration 19.6 g of the desired product (yield : 70%).

N.M.R: DMSO <sup>1</sup>H δ (ppm) : 3.8 (s,3H); 4.45 (d,2H); 6.5-6.6 (m,3H); 7.3-7.45 (m,3H);  
25       7.8-7.95 ( m,3H); 8.9 (t,1H)

**Purity (HPLC) : 99.1 %**

#### **Step 2 : Methyl 4-(6-iodo-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoate**



To a solution of 21.35 g (52 mmol) of the compound obtained in Step 1 in 400 ml of dry tetrahydrofuran were added 9.3 g (57.2 mmol) of 1,1'-carbonyldiimidazole. The solution was heated overnight to 60°C. After cooling the precipitate was filtered and dried to afford 19.6 g of the desired product (yield : 68.3%).

5 N.M.R: DMSO <sup>1</sup>H δ (ppm) : 3.8 (s,3H); 5.1 (s,2H); 6.95-7.05 (m,1H); 7.35-7.45 (m,2H); 7.8-7.90 (m,2H) ; 7.9-8.0 (m,1H) ; 8.2 (s,1H) ; 11.6 (bs,1H)

Purity (HPLC) : 99.5 %

**Step 3 : Methyl 4-(6-iodo-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl) -benzoate**

10 To a stirred suspension of 11 g (25.2 mmol) of the compound obtained in Step 2 and 110 ml of dry DMF were added 5.22 g (37.8 mmol) of K<sub>2</sub>CO<sub>3</sub>, at room temperature. After 15 minutes, 7.85 ml (17.9 g, 126 mmol) of iodomethane were added. The reaction mixture was stirred for 2 hours and the precipitate filtered off and dissolved in a mixture of dichloromethane/methanol. The organic phase was washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>  
15 and concentrated to afford a precipitate corresponding to the desired product (10.1 g ; yield : 89%).

N.M.R: DMSO <sup>1</sup>H δ (ppm) : 3.5 (s,3H) ; 3.8 (s,3H) ; 5.2 (s,2H) ; 7.30 (d,1H) ; 7.45 (d,2H) ; 7.90 (d,2H) ; 8.1 (d,1H) ; 8.3 (s,1H)

Purity (HPLC) : 96.7 %

**Step 4 : 4-(6-Iodo-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid**

20 A mixture of 3.0 g (6.66 mmol) of the compound obtained in Step 3, 30 ml of dioxane, 120 ml H<sub>2</sub>O, and 0.56 g (13.3 mmol) of LiOH.H<sub>2</sub>O was heated to reflux over 1 hour. After cooling and acidification with concentrated hydrochloric acid, the precipitate obtained was filtered off and recrystallized in dioxane/ether to afford 1.85 g of the desired product (yield : 64.2%).

25 N.M.R: DMSO <sup>1</sup>H δ (ppm) : 3.5 (s,3H) ; 5.2 (s,2H) ; 7.30 (d,1H) ; 7.40 (d,2H) ; 7.85 (d,2H) ; 8.1 (d,1H) ; 8.30 (s,1H) ; 12.9 (bs,1H)

Purity (HPLC) : 98.0 %

**Preparation B : 4-(1-Methyl-2,4-dioxo-6-trifluoromethanesulfonyloxy-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl)-benzoic acid**

**Step 1 : 5-(tert-Butoxycarbonylamino)-2-methoxypyridine-4-carboxylic acid**

The compound 5-(tert-butoxycarbonylamino)-2-methoxypyridine-4-carboxylic acid was prepared using the procedure described in *J. Chem. Soc., Perkin Trans I*, 1996, 18, 2221-2226.

**Step 2 : Methyl 4-(((5-tert-butoxycarbonylamino-2-methoxy-pyridine-4-carbonyl)-amino)-methyl)-benzoate**

9 g (33.5 mmol) of the compound obtained in Step 1, 320 ml of dichloromethane, 11 g (33.5 moles) of TOTU and 6.1 g (36.9 mmol) of methyl-(4-aminomethyl)benzoate were stirred and cooled to 0°C, and then 11.6 ml (8.6g, 67 mmol) of diisopropylamine added. The mixture was stirred for 15 minutes at 0°C and then overnight at room temperature. The reaction mixture was washed successively with 200 ml NH<sub>4</sub>OH, 200 ml H<sub>2</sub>O, 200 ml HCl 10%, 200 ml H<sub>2</sub>O, 200 ml NaHCO<sub>3</sub>, and 200 ml H<sub>2</sub>O. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was crystallized in a mixture of dichloromethane/ether to afford 10.5 g of the desired product (yield : 73.3 %).

TLC : CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 95/5 v/v R<sub>f</sub> = 0.60

N.M.R: CDCl<sub>3</sub> <sup>1</sup>H δ (ppm) : 1.50 (s,9H) ; 3.90 (2s,6H) ; 4.60 (d,2H) ; 6.70 (s,1H) ; 7.0 (bs,1H) ; 7.4 (d,2H) ; 8.0 (d,2H) ; 8.75 (bs,1H) ; 8.9 (s,1H)

**Step 3 : Methyl 4-(((5-amino-2-methoxy-pyridine-4-carbonyl)-aminomethyl)-benzoate**

To a solution of 4.8 g (11.5 mmol) of the compound obtained in Step 2 in 100 ml of dichloromethane were added 20 ml of trifluoroacetic acid. The reaction was heated to 40°C for 1 hour, and then concentrated under vacuum. The residue was taken up in a mixture of dichloromethane and H<sub>2</sub>O then basified with NaOH. After separation by decantation, the organic phase was washed, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to afford 3.5 g of a yellow precipitate corresponding to the desired product (yield : 97%).

TLC : CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 v/v R<sub>f</sub> = 0.40

N.M.R:  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm) : 3.8 (s,3H) ; 3.9 (s,3H) ; 4.6 (d,2H) ; 4.7 (s,2H) ; 6.7 (s,1H) ; 6.75-6.85 (m,1H) ; 7.40 (d,2H) ; 7.75 (s,2H) ; 8.0 (d,2H)

**Step 4 :** Methyl 4-(6-methoxy-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]-pyrimidin-3-ylmethyl)-benzoate

5 To a solution of 2.5 g (7.9 mmol) of the compound obtained in Step 3 in 110 ml of dry THF were added 2 g (12.4 mmol) of 1,1'-carbonyldiimidazole. The reaction mixture was heated to 60°C for 24 hours. After cooling, 50 ml  $\text{H}_2\text{O}$  were added and the mixture was stirred for 30 minutes to 0°C. The precipitate was filtered and washed successively with  $\text{H}_2\text{O}$ , MeOH and dichloromethane to afford 2.38 g of the desired product (yield : 88.3%).

10 TLC :  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95/5 v/v  $R_f$  = 0.45

N.M.R: DMSO  $^1\text{H}$   $\delta$  (ppm) : 3.80 (s,3H) ; 3.90 (s,3H) ; 5.10 (s,2H) ; 7.2 (s,1H) ; 7.45 (d,2H) ; 7.90 (d,2H) ; 8.25 (s,1H) ; 11.6 (s,1H)

**Step 5 :** Methyl 4-(6-methoxy-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl)-benzoate

15 2.38 g (7 mmol) of the compound obtained in Step 4 and 52 ml of dry DMF were stirred and heated until dissolution. After cooling to 25°C, 1.45 g (10 mmol) of  $\text{K}_2\text{CO}_3$  and 2.2 ml (5.7 g, 35 mmol) of iodomethane were added. The mixture was stirred for 30 minutes at room temperature, then concentrated under vacuum. The residue was treated with  $\text{H}_2\text{O}$  and the precipitate filtered off, washed with methanol, then dissolved in dichloromethane. The organic phase was washed with  $\text{H}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. The product was crystallised in ether and filtered to afford 2.0 g of the desired product (yield : 80%).

20 TLC :  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95/5 v/v  $R_f$  = 0.95

Purity (HPLC) : 98.5%

25 N.M.R: DMSO  $^1\text{H}$   $\delta$  (ppm) : 3.50 (s,3H) ; 3.80 (s,3H) ; 3.90 (s,3H) ; 5.20 (s,2H) ; 7.3 (s,1H) ; 7.45 (d,2H) ; 7.90 (d,2H) ; 8.50 (s,1H)

**Step 6 :** 4-(6-Hydroxy-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl)-benzoic acid

1.4 g (3.93 mmol) of compound obtained in Step 5, and 14 ml of hydrobromic acid were heated to reflux for 1 hour. After cooling, 30 ml of H<sub>2</sub>O were added and the precipitate was filtered off and washed with H<sub>2</sub>O and MeOH to afford 1.1 g of the desired product (yield : 85.5%)

5     **TLC** : CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10 v/v R<sub>f</sub> = 0.10

**N.M.R** : DMSO <sup>1</sup>H δ (ppm) 3.50 (s,3H); 5.20 (s,2H); 7.05 (s,1H); 7.40 (d,2H); 7.90 (d,2H); 8.20 (s,1H); 10.4-13.0 (bs,2H)

**Step 7 :**    4-(1-Methyl-2,4-dioxo-6-trifluoromethanesulfonyloxy-1,4-dihydro-2H-pyrido[3,4-*d*]pyrimidin-3-ylmethyl)-benzoic acid

10     A solution of 1.2 g of compound obtained in Step 6 in 14 ml of dry pyridin was stirred and cooled to 0°C, and then 1.5 ml (2.52 g, 9 mmol) of trifluoromethanesulfonic anhydride were added. The reaction was allowed to stir at 0°C for 30 minutes then quenched with 30 ml of H<sub>2</sub>O and dichloromethane. The organic phase was washed with H<sub>2</sub>O, HCl 10%, and H<sub>2</sub>O. After concentration the residue was crystallised in a mixture dichloromethane/ether  
15     to afford 0.5 g of the desired product (yield : 30%).

**TLC** : CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10 v/v R<sub>f</sub> = 0.55

**N.M.R**: DMSO <sup>1</sup>H δ (ppm): 3.55 (s,3H); 5.20 (s,2H); 7.45 (d,2H); 7.90 (d,2H); 8.10 (s,1H); 8.80 (s,1H); 12.9 (bs,1H)

20     **Preparation C :** Methyl    4-(5-oxo-7-(Trifluoromethylsulfonyloxy)-5H-[1,2,4]triazolo [4,3-*a*]quinazolin-4-ylmethyl)-benzoate

**Step 1 :**    4-Benzyl-7-(trifluoromethylsulfonyloxy)-4H-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one

25     To a suspension of 41.3 g (141.3 mmol) of 4-benzyl-7-hydroxy-4H-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (obtained as described in WO 00/66584) in 500 ml of CH<sub>2</sub>Cl<sub>2</sub>, 25 g (148.3 mmol) of trifluoromethylsulfonylchloride were added under stirring. Then, 22.5 g (222.5 mmol) of triethylamine were added dropwise while maintaining the internal temperature between 15 and 20°C. After the completion of addition, stirring was continued at room temperature for 4 hours. After removal of the insoluble solid by filtration, the  
30     organic solution was washed with water and brine, then dried over Na<sub>2</sub>SO<sub>4</sub> and

concentrated, providing 33.1 g of crude solid, which was purified by chromatography (cyclohexane/AcOEt: 25/75 v/v) to afford 22.5 g of the desired compound (yield : 37.5%).

TLC : CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 v/v R<sub>f</sub> = 0.45

**Step 2 : 7-(Trifluoromethylsulfonyloxy)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one**

5 A suspension of 10.0 g (23.5 mmol) of the compound obtained in Step 1 and 18.8 g (141 mmol) of aluminium chloride in 200 ml anhydrous benzene was heated at 50°C, under stirring, for 1h30. After cooling, the mixture obtained was poured on water/ice. After stirring and homogenization, the insoluble solid was isolated by filtration, washed with several portions of water until neutral pH and dried, then finally washed with a portion of

10 CH<sub>2</sub>Cl<sub>2</sub>, leaving 7.95 g (99%) of the desired compound.

TLC : CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 v/v R<sub>f</sub> = 0.10

**Step 3 : Methyl 4-(5-oxo-7-(Trifluoromethylsulfonyloxy)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoate**

15 To a stirred solution of 7.9 g (24.3 mmol) of the compound obtained in Step 2 in 100 ml of DMF were added 7.93 g (24.3 mmol) of cesium carbonate, and then 5.56 g (24.3 mmol) of methyl 4-(bromomethyl)benzoate. The mixture was stirred overnight and the solvent was removed under vacuum. The resulting residue was partitioned between H<sub>2</sub>O and a mixture of dichloromethane and ethyl acetate. A first portion (5.9 g) of product insoluble in the two

20 phases was obtained by filtration then recrystallized in methanol to give 4.85 g of the pure title compound. The organic phase was separated, washed with water and brine, and dried over anhydrous sodium sulfate. Concentration under reduced pressure afforded 4.5 g of crude product that was recrystallized in methanol to provide 2.2 g of pure compound. An additional portion of 2.5 g was finally obtained after column chromatography on silica gel

25 of the residues gathered from the organic phases (dichloromethane/methanol 98/2 v/v). All in all, 9.55 g (yield : 81.5%) of the desired product were obtained.

TLC : CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 95/5 v/v R<sub>f</sub> = 0.35

**Preparation D : 4-(5-oxo-7-(Trifluoromethylsulfonyloxy)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid**

**Step 1 :** *tert*-Butyl 4-(5-oxo-7-(Trifluoromethylsulfonyloxy)-5*H*-[1,2,4]triazolo  
[4,3-*a*]quinazolin-4-ylmethyl)-benzoate

The product is obtained with a yield of 60.5% (0.95 g) according to the procedure of Step 3  
of Preparation C using 1.0 g (2.99 mmol) of compound obtained in Step 1 of Preparation C  
5 and 0.81 g (2.99 mmol) of *tert*-butyl-4-(bromomethyl)benzoate.

**Step 2 :** 4-(5-oxo-7-(Trifluoromethylsulfonyloxy)-5*H*-[1,2,4]triazolo[4,3-*a*]  
quinazolin-4-ylmethyl)-benzoic acid

To a suspension of 0.27 g (0.515 mmol) of compound obtained in Step 1 in 30 ml of  
dichloromethane, 2.7 ml of trifluoroacetic acid were added and stirring was continued at  
10 room temperature for 16 hours. The reaction mixture was poured into water and the  
resulting mixture stirred for 15 minutes. The ensuing precipitate was filtered off, washed  
with water until neutral pH and dried at 50°C under vacuum to provide 0.21 g of the  
desired product.

TLC : dichloromethane/methanol 90/10 v/v R<sub>f</sub> = 0.30

15 **Example 1 :** Methyl 4-{6-[3-(4-methoxyphenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-  
dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate

To a stirred suspension of 1.5 g (3.33 mmol) of compound obtained in Step 3 of  
Preparation A in 110 ml of triethylamine were added, under nitrogen atmosphere, 0.6 g (4  
mmol) of 3-(4-methoxyphenyl)-prop-1-yne (described in the literature:  
20 *J.Prakt.Chem.*, 1966, 33, 84-95) in 10 ml of triethylamine, 47 mg (0.06 mmol) of  
dichlorobis(triphenylphosphine)palladium (II) and 26 mg (0.13 mmol) of CuI. The mixture  
was heated to 60°C over 3 hours (uncomplete reaction). The mixture was then concentrated  
under vacuum and the residue purified by flash chromatography to afford 0.130 mg of the  
desired product (yield : 6%) which was crystallized in a mixture of  
25 dichloromethane/methanol.

TLC : CH<sub>2</sub>Cl<sub>2</sub>/Acetone 99/1 v/v R<sub>f</sub> = 0.9

N.M.R: DMSO <sup>1</sup>H δ (ppm) ; 3.5 (s,3H); 3.75 (s,3H); 3.8 (s,5H); 5.2 (s,2H); 6.9 (d,2H);  
7.35 (s,2H); 7.45 (m,3H); 7.85 (d,1H); 7.9 (d,2H); 8.0 (s,1H)

IR : 2361, 1702, 1656, 1612, 1508, 1475, 1279, 1249, 117, 1102, 958, 805 cm<sup>-1</sup>

**Mp** = 168.5°C

**Purity (HPLC)** : 97.9 %

**Example 2 : 4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

- 5 To a stirred solution of 0.68 g (1.56 mmol) of compound obtained in Step 4 of Preparation A in 6.8 ml of dry DMF, were added successively, under nitrogen atmosphere, 1.2 ml (0.8 g, 6.24 mmol) of diisopropylethylamine, 56.8 mg (0.078 mmol) of dichlorobis (triphenylphosphine)palladium (II), a catalytic amount of CuI and 0.273 ml (0.253 g, 2.18 mmol) of 3-phenyl-1-propyne. The reaction mixture was heated to 50°C over  
10 approximately 4 hours. Then, the mixture is concentrated under vacuum and the residue purified by flash chromatography (dichloromethane/MeOH 90/10 v/v) to afford, after crystallization in a mixture of dichloromethane/ether, 0.270 g of the desired product (yield : 40.8%).

**TLC** : CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9/1 v/v R<sub>f</sub> = 0.50

- 15 **N.M.R.**: DMSO <sup>1</sup>H δ (ppm) ; 3.5 (s,3H); 3.9 (s,2H); 5.2 (s,2H); 7.20-7.50 (m,8H); 7.80 (m,3H); 8.05 (s,1H); 12.8 (bs,1H);

**IR** : 2894, 1700, 1660, 1616, 1508, 1314, 1295, 1097, 825, 795, 747 cm<sup>-1</sup>

**Mp** = 258 °C

**Purity (HPLC)** : 98.6 %

- 20 **Example 3 : 4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid**

This compound was obtained according to the procedure described in Example 2 using as reagent 3-(4-methoxyphenyl)-prop-1-ynyl. The crude product was crystallized in dioxane to afford the desired compound.

- 25 **TLC** : CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9/1 v/v R<sub>f</sub> = 0.50

**N.M.R.**: DMSO <sup>1</sup>H δ (ppm) ; 3.55 (s,3H); 3.75 (s,3H); 3.8 (s,2H); 5.15 (s,2H); 6.9 (d,2H); 7.30 (d,2H); 7.40 (m,3H); 7.85 (m,3H); 8.00 (s,1H); 12.85 (bs,1H);

**IR** : 2646, 1687, 1659, 1508, 1477, 1422, 1325, 1242, 1177, 1040, 950, 812 cm<sup>-1</sup>

**Mp** = 262 °C

**Purity (HPLC)** : 95.4 %

**Example 4 :** 4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid

5 To a stirred solution of 0.1 g (0.22 mmol) of the compound of Preparation B in 1 ml of dry DMF were added successively 0.2 ml (0.14 g, 1.1 mmol) of diisopropylethylamine, 9 mg (0.012 mmol) of dichlorobis(triphenylphosphine)palladium (II), a catalytic amount of CuI and 0.046 ml (0.043 g, 1.1 mmol) of 3-phenyl-1-propyne. The reaction was stirred overnight at room temperature and then H<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub> were added. The organic layer  
10 was separated and washed with HCl 10% and H<sub>2</sub>O, then dried over sodium sulfate and concentrated under vacuum. The residue was crystallized in a mixture of dichloromethane/ether to afford 0.040 g of the desired product (yield : 43%).

**TLC** : CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9/1 v/v R<sub>f</sub> = 0.50

**N.M.R.**: DMSO <sup>1</sup>H δ (ppm) ; 3.6 (s,3H); 3.95 (s,2H); 5.2 (s,2H); 7.20-7.50 (m,7H); 7.80-  
15 7.95 (m,2H); 7.95 (s,1H); 8.90 (s,1H); 12.8 (bs,1H)

**IR** : 1720, 1695, 1678, 1612, 1490, 1279, 1100, 759, 732 cm<sup>-1</sup>

**Mp** = 236.2 °C

**Purity (HPLC)** : 96.7 %

**Example 5:** 4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-*d*]pyrimidin-3-ylmethyl}-benzoic acid  
20

The compound is obtained according to the procedure described in Example 4 using the compound of Preparation B and the 3-(4-methoxyphenyl)-prop-1-yne.

**TLC** : CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9/1 v/v R<sub>f</sub> = 0.60

**N.M.R.**: DMSO <sup>1</sup>H δ (ppm); 3.60 (s,3H); 3.75 (s,3H); 3.85 (s,2H); 5.20 (s,2H); 6.9-7.0  
25 (m,2H); 7.30-7.40 (m,2H); 7.45-7.50 (m,2H); 7.80-7.90 (m,3H); 8.90 (s,1H); 12.9 (bs,1H)

**IR** : 1721, 1670, 1511, 1477, 1421, 1325, 1245, 1178, 1037, 792 cm<sup>-1</sup>

**Mp** = 262 °C

**Purity (HPLC)** : 95.9 %



**Example 6 : 4-Benzyl-7-(3-phenyl-prop-1-ynyl)-4*H*-[1,2,4]triazolo[4,3-*a*]  
quinazolin-5-one**

To a suspension of 1.5 g (3.53 mmol) of compound obtained in Step 1 of Preparation C in 12 ml of DMF were added, under inert atmosphere of nitrogen, 0.574 g (4.94 mmol) of 3-phenylprop-1-yne, 1.45 g (14.4 mmol) of triethylamine and 0.1 g of dichlorobis (triphenylphosphin)palladium (II). The reaction mixture was then stirred and heated at 50°C for 5 hours. After cooling at room temperature, H<sub>2</sub>O was added and the mixture extracted several times with AcOEt. The organic phase was washed with water and brine and then dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated, leaving 1.5 g of crude solid that was chromatographed on a silica column (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 98.5/1.5 v/v) to afford 0.25 g (yield : 18%) of an off-white solid pure in TLC. A sample was purified by recrystallization in methanol.

**Mp** = 238°C

**N.M.R.** DMSO <sup>1</sup>H δ (ppm): 3.85 (s, 2H); 5.55 (s, 2H); 7.25-7.45 (m, 8H); 7.6 (d, 1H); 7.65-7.75 (m, 2H); 7.85 (d, 1H); 8.5 (s, 1H); 8.7 (s, 1H).

**Example 7 : 4-Benzyl-7-[(4-methoxyphenyl)-prop-1-ynyl]-4*H*-[1,2,4]-triazolo[4,3-*a*]  
quinazolin-5-one**

The compound was obtained according to the procedure described in Example 6 using the same substrate (Preparation C, Step 1) and 0.48 g of 3-(4-methoxyphenyl)-prop-1-yne. The crude product was purified by chromatography on a silica column (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 98/2 v/v). A treatment of the resultant solid with boiling AcOEt gave 0.15 g (yield : 15%) of an off-white solid pure in TLC.

**Mp** = 267°C

**N.M.R.** CDCl<sub>3</sub> <sup>1</sup>H δ (ppm): 3.8 (s, 2H); 3.8 (s, 3H); 5.5 (s, 2H); 6.9 (d, 2H); 7.2-7.35 (m, 5H); 7.6 (d, 1H); 7.68 (d, 2H); 7.8 (d, 1H); 8.4 (s, 1H); 8.7 (s, 1H).

**Example 8 : Methyl 4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5*H*-  
[1,2,4]triazolo[4,3-*a*]quinazolin-4-ylmethyl}-benzoate**

The compound was obtained according to the procedure described in Example 6 using the compound of the Preparation C Step 3, 1.1 g of 3-(4-methoxyphenyl)prop-1-yne, and 2.72 g of N-ethyl-N,N-diisopropylamine. The crude product was purified by chromatography on a silica column (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 98/2 v/v). A treatment of the resultant solid with boiling AcOEt gave 1.5 g (yield : 59%) of an off-white solid pure in TLC.

**Mp** = 249°C

**N.M.R:** CDCl<sub>3</sub> <sup>1</sup>H δ (ppm): 3.79 (s, 2H); 3.81 (s, 3H) ; 3.88(s, 3H) ; 5.56 (s, 2H) ; 6.89 (d, 2H) ; 7.30 (d, 2H) ; 7.60 (d, 1H) ; 7.70 (d, 2H) ; 7.82 (d, 1H) ; 7.97 (d, 2H) ; 8.44 (s, 1H) ; 8.7 (s, 1H).

**Example 9 : 4-[5-Oxo-7-(3-phenyl-prop-1-ynyl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl]-benzoic acid**

The compound was obtained according to the procedure described in Example 6 using the compound of the Preparation D (0.195 g), 0.067 g of 3-phenylprop-1-yne, and 0.215 g of N-ethyl-N,N-diisopropylamine. The crude product was purified by chromatography on a silica column (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 90/10 then 85/15 v/v) to afford 0.14 g (yield : 77%) of an off-white solid pure in TLC corresponding to the desired product.

**Mp** = 262°C

**N.M.R:** DMSO <sup>1</sup>H δ (ppm): 3.96 (s, 2H); 5.42 (s, 2H); 7.27 (t, 1H); 7.37 (t, 2H); 7.44 (d, 2H); 7.52 (d, 2H); 7.87 (d, 2H); 8.02 (d, 1H); 8.18-8.22 (m, 2H); 9.53 (s, 1H); 12.5-13.2 (m, 1H).

**Example 10 : 4-(1-Methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid**

The compound was obtained according to the procedure described in Example 5 using the compound of the Preparation A Step 4 (0.59 g, 1.35 mmol), 0.193 g (1.89 mmol) of 1-phenyleth-1-yne, 0.050 g of dichlorobis(triphenylphosphine)palladium, a catalytic amount of CuI and 0.700 g (5.4 mmol) of N-ethyl-N,N-diisopropylamine. The crude

product was purified by crystallization in dichloromethane provided 0.55 g (yield : 100%) of an off-white solid pure in TLC.

Mp = 260°C

N.M.R: DMSO <sup>1</sup>H δ (ppm): 3.55 (s, 3H) ; 5.21 (s, 2H) ; 7.36-7.50 (m, 5H) ; 7.50-7.65 (m, 3H) ; 7.82-7.99 (m, 3H) ; 8.16 (s, 1H) ; 12.7-13.1 (m, 1H).

### **PHARMACOLOGICAL STUDIES OF COMPOUNDS OF THE INVENTION**

#### **Example 11 : Evaluation of the in vitro activity of the MMP-13 inhibitor compounds according to the invention.**

The inhibitory activity of the compounds of formula (I) according to the invention with respect to matrix metalloprotease-13 is evaluated by testing the ability of the compounds of the invention to inhibit the proteolysis of a peptide substrate with MMP-13.

The peptide substrate used in the test is the following peptide: Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-OEt.

The inhibitory activity of a compound of formula (I) according to the invention is expressed as the IC<sub>50</sub> value, which is the concentration of inhibitor for which an inhibition of 50% of the activity of the matrix metalloprotease under consideration is observed.

To carry out this test, a reaction medium of 100 µl volume is prepared, containing: 50 mM of HEPES buffer, 10 mM of CaCl<sub>2</sub> and 1 mM of 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB), and 100 µM of substrate, the pH being adjusted to 7.0.

Increasing concentrations of the inhibitory compound present in a 2.0% DMSO solution and 2.5 nM of the catalytic domain of human MMP-13 are added to the test samples.

The concentrations of inhibitors present in the test samples range from 100 µM to 0.5 nM.

The measurement of the proteolysis of the substrate peptide is monitored by measuring the absorbance at 405 nm using a spectrophotometer for reading microplates, at the laboratory temperature, the measurements being carried out continuously for 10 to 15 minutes.

The IC<sub>50</sub> values are calculated from a curve in which the percentage of the catalytic activity relative to the control is represented on the X-axis and the concentration of inhibitor is represented on the Y-axis.

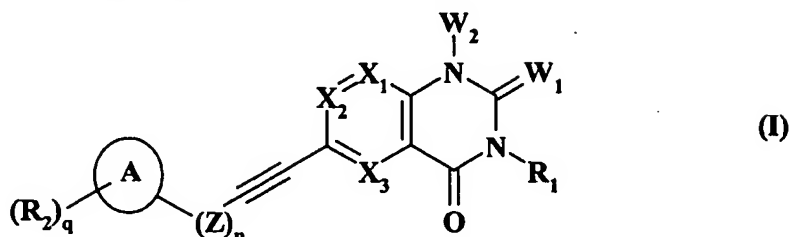
The IC<sub>50</sub> values on MMP-13 of the compounds of Examples 1 to 10 are all below 1  $\mu$ M.

The test described above for the inhibition of MMP-13 was also adapted and used to determine the ability of the compounds of formula (I) to inhibit the matrix metalloproteases MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14.

- 5 The results obtained show that the compounds according to the invention generally have IC<sub>50</sub> values for MMP-13 which are about 100 times lower than the IC<sub>50</sub> values for the same compounds with respect to the other matrix metalloproteases tested.

CLAIMS

I- A compound selected from those of formula (I) :



5 wherein :

W<sub>1</sub> represents an oxygen atom, a sulfur atom, or a -NR<sub>3</sub> group in which R<sub>3</sub> represents hydrogen atom, (C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxyl or cyano,

W<sub>2</sub> represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono(C<sub>1</sub>-C<sub>10</sub>)alkylamino, di(C<sub>1</sub>-C<sub>10</sub>)alkylamino, each alkyl moiety being identical or different,
- (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)alkenyl, (C<sub>3</sub>-C<sub>6</sub>)alkynyl, (C<sub>5</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl(C<sub>1</sub>-C<sub>10</sub>)alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected from halogen, amino, mono(C<sub>1</sub>-C<sub>10</sub>)alkylamino, di(C<sub>1</sub>-C<sub>10</sub>)alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)acyl, -C(=O)OR<sub>4</sub>, -OR<sub>4</sub> and -SR<sub>4</sub>, R<sub>4</sub> representing a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

20 or W<sub>1</sub> and W<sub>2</sub> form together a group of formula N-X<sub>4</sub>=W<sub>3</sub> (in which the nitrogen atom is bonded on the place of the group W<sub>1</sub> and the group W<sub>3</sub> is bonded on the place of the group W<sub>2</sub>) wherein:

- W<sub>3</sub> represents a nitrogen atom or a group -CR<sub>5</sub> in which R<sub>5</sub> is selected from :
  - a hydrogen atom,

- $-OR_6$ ,  $-SR_6$  in which  $R_6$  is selected from hydrogen,  $(C_1-C_6)$ alkyl and  $(C_5-C_{10})$ aryl $(C_1-C_{10})$ alkyl;
  - $(C_1-C_6)$ alkyl,  $(C_3-C_{10})$ cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen,  $(C_5-C_{10})$ aryl,  $(C_5-C_{10})$ heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and  $(C_5-C_{10})$ aryl $(C_1-C_{10})$ alkyl, these groups being optionally substituted by  $-(CH_2)_p-OH$  or  $-(CH_2)_p-NH_2$ , wherein  $p$  is an integer from 0 to 4 inclusive,
  - $X_4$  represents a nitrogen atom or a group  $-CR_7$  in which  $R_7$  is selected from hydrogen,  $-NR_8R_9$ ,  $-OR_8$ ,  $-SR_8$ ,  $(C_1-C_6)$ alkyl,  $(C_3-C_{10})$ cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen,  $(C_5-C_{10})$ aryl,  $(C_5-C_{10})$ heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and  $(C_5-C_{10})$ aryl $(C_1-C_{10})$ alkyl, these groups being optionally substituted by  $-(CH_2)_p-OH$  or  $-(CH_2)_p-NH_2$  wherein  $p$  is an integer from 0 to 4 inclusive,
- and in which  $R_8$  and  $R_9$ , identical or different, are selected from hydrogen,  $(C_1-C_6)$ alkyl and  $(C_5-C_{10})$ aryl $(C_1-C_{10})$ alkyl,

$X_1$ ,  $X_2$  and  $X_3$  represent, independently of each other, a nitrogen atom or a carbon atom, the said carbon atom being unsubstituted or substituted with a group selected from :

- $(C_1-C_6)$ alkyl, hydroxyl,  $(C_1-C_6)$ alkoxy, halogen, trifluoromethyl, cyano, nitro,
- $-S(O)_{n_1}R_4$  wherein  $n_1$  represents an integer from 0 to 2 inclusive and  $R_4$  represents an hydrogen atom or a  $(C_1-C_6)$ alkyl group,
- and  $-NR_{10}R_{11}$  wherein  $R_{10}$  and  $R_{11}$ , which may be identical or different, represent a group selected from hydrogen atom,  $(C_1-C_6)$ alkyl, and  $(C_5-C_{10})$ aryl $(C_1-C_{10})$ alkyl, or  $R_{10}$  and  $R_{11}$  form together with the nitrogen atom to which there are bonded, a 5- or 6-ring members which can optionally contain a second hetero atom selected from nitrogen and oxygen,

with the proviso that not more than two of the groups  $X_1$ ,  $X_2$  and  $X_3$  simultaneously represent a nitrogen atom,

$n$  is an integer from 0 to 8 inclusive,

Z represents  $-CR_{12}R_{13}$ , wherein  $R_{12}$  and  $R_{13}$  independently of each other, represent a group selected from hydrogen,  $(C_1-C_6)$ alkyl, trihalogeno $(C_1-C_6)$ alkyl, halogen, amino, mono $(C_1-C_6)$ alkylamino, di $(C_1-C_6)$ alkylamino in which each alkyl moiety is identical or different,  $-OR_4$ ,  $-SR_4$ , and  $-C(=O)OR_4$ ,  $R_4$  being as defined hereinbefore, or  $-CR_{12}R_{13}$  form together a carbonyl group, and

-when n is greater than or equal to 2, the hydrocarbon chain Z optionally contains one or more multiple bonds,

-and/or one of the carbon atoms in the hydrocarbon chain Z may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted or substituted with a  $(C_1-C_6)$ alkyl,

A represents the residue of an aromatic or non-aromatic 5- or 6-membered monocycle comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, or a bicycle composed of two aromatic or non-aromatic 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur,

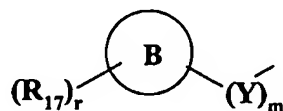
the group(s)  $R_2$ , which may be identical or different, are selected from hydrogen,  $(C_1-C_6)$ alkyl, halogen, cyano, nitro, trihalogeno $(C_1-C_6)$ alkyl,  $-NR_{10}R_{11}$ ,  $-OR_{14}$ ,  $-SR_{14}$ ,  $-SOR_{14}$ ,  $-SO_2R_{14}$ ,  $(C_1-C_6)$ acyl,  $-(CH_2)_kNR_{10}R_{11}$ ,  $-X_5(CH_2)_kNR_{10}R_{11}$ ,  $-(CH_2)_kSO_2NR_{14}R_{15}$ ,  $-X_5(CH_2)_kC(=O)OR_{14}$ ,  $-(CH_2)_kC(=O)OR_{14}$ ,  $-X_5(CH_2)_kC(=O)NR_{14}R_{15}$ ,  $-(CH_2)_kC(=O)NR_{14}R_{15}$  and  $-X_6-R_{16}$  in which :

- $X_5$  represents an oxygen atom, a sulfur atom, a  $-NH$  group, or a  $-N(C_1-C_6)$ alkyl group,
- k is an integer from 0 and 3 inclusive,
- $R_{10}$  and  $R_{11}$  are as defined hereinbefore,
- $R_{14}$  and  $R_{15}$ , identical or different, represent hydrogen or  $(C_1-C_6)$ alkyl,
- $X_6$  represents a single bond,  $-CH_2-$ , an oxygen atom or a sulfur atom which is unsubstituted or substituted with one or two oxygen atoms,
- $R_{16}$  represents the residue of an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring which is unsubstituted or substituted with one or

more groups, which may be identical or different, selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, trihalogeno(C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, mercapto, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino each alkyl moiety being identical or different, and when the ring is heterocyclic, it comprises from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur,

q is an integer from 0 to 7 inclusive,

R<sub>1</sub> represents a group selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)alkenyl, and (C<sub>3</sub>-C<sub>6</sub>)alkynyl, the groups alkyl, alkenyl and alkynyl being optionally substituted with one or more groups, which may be identical or different, selected from amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino in which each alkyl moiety is identical or different, (C<sub>1</sub>-C<sub>6</sub>)alkyl, cyano, trihalogeno(C<sub>1</sub>-C<sub>6</sub>)alkyl, -C(=O)OR<sub>4</sub>, -OR<sub>4</sub>, -SR<sub>4</sub>, in which R<sub>4</sub> is as defined above, and the group of formula :



in which:

- m is an integer from 0 to 8 inclusive,
- Y represents -CR<sub>18</sub>R<sub>19</sub>, wherein R<sub>18</sub> and R<sub>19</sub> independently of each other, represent a group selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, phenyl, trihalogeno(C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino in which each alkyl moiety is identical or different, -OR<sub>4</sub>, -SR<sub>4</sub> or -C(=O)OR<sub>4</sub> wherein R<sub>4</sub> is as defined above, and
  - when m is greater than or equal to 2, the hydrocarbon chain Y optionally contains one or more multiple bonds,
  - and/or one of the carbon atoms in the hydrocarbon chain Y may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted or substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl,
- B represents a group selected from the residue of an aromatic or non-aromatic, 5- or 6-membered monocycle comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and a bicycle, composed of two aromatic or non-aromatic, 5- or 6-



membered rings, which may be identical or different, comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur,

- r is an integer from 0 to 7 inclusive,
- the group(s) R<sub>17</sub> which may be identical or different are selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, cyano, nitro, trihalogeno(C<sub>1</sub>-C<sub>6</sub>)alkyl, -NR<sub>10</sub>R<sub>11</sub>, -OR<sub>14</sub>, -SR<sub>14</sub>, -SOR<sub>14</sub>, -SO<sub>2</sub>R<sub>14</sub>, (C<sub>1</sub>-C<sub>6</sub>)acyl, -(CH<sub>2</sub>)<sub>k</sub>NR<sub>10</sub>R<sub>11</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>NR<sub>10</sub>R<sub>11</sub>, -(CH<sub>2</sub>)<sub>k</sub>SO<sub>2</sub>NR<sub>14</sub>R<sub>15</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>14</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>14</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>14</sub>R<sub>15</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>14</sub>R<sub>15</sub> and the group of formula -X<sub>6</sub>-R<sub>16</sub> in which X<sub>5</sub>, k, R<sub>10</sub>, R<sub>11</sub>, R<sub>14</sub>, R<sub>15</sub>, X<sub>6</sub> and R<sub>16</sub> are as defined hereinbefore, and

optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

2- A compound according to claim 1, wherein :

W<sub>1</sub> represents an oxygen atom, a sulfur atom, or a -NR<sub>3</sub> group in which R<sub>3</sub> represents hydrogen atom, (C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxyl or cyano,

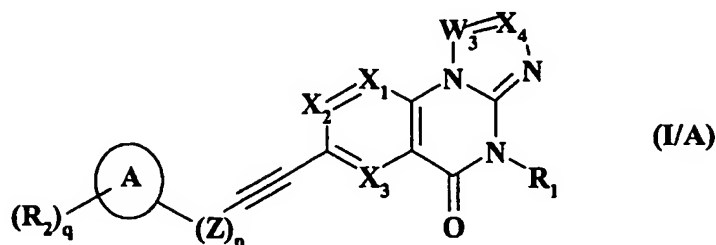
W<sub>2</sub> represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono(C<sub>1</sub>-C<sub>10</sub>)alkylamino, di(C<sub>1</sub>-C<sub>10</sub>)alkylamino, each alkyl moiety being identical or different,
- (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)alkenyl, (C<sub>3</sub>-C<sub>6</sub>)alkynyl, (C<sub>5</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl(C<sub>1</sub>-C<sub>10</sub>)alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected from halogen, amino, mono(C<sub>1</sub>-C<sub>10</sub>)alkylamino, di(C<sub>1</sub>-C<sub>10</sub>)alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)acyl, -C(=O)OR<sub>4</sub>, -OR<sub>4</sub> and -SR<sub>4</sub>, R<sub>4</sub> representing a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

and X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, R<sub>1</sub>, R<sub>2</sub>, A, Z, n and q are as defined in formula (I),

optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

3- A compound according to claim 1 in which it represents a compounds of formula (IA) :



wherein

W<sub>3</sub> represents a nitrogen atom or a group -CR<sub>5</sub> in which R<sub>5</sub> is selected from :

- 5           - a hydrogen atom,
- -OR<sub>6</sub>, -SR<sub>6</sub> in which R<sub>6</sub> is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl;
- (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C<sub>5</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>10</sub>)heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl, these groups being optionally substituted by -(CH<sub>2</sub>)<sub>p</sub>-OH or -(CH<sub>2</sub>)<sub>p</sub>-NH<sub>2</sub>, wherein p is an integer from 0 to 4 inclusive,

15           X<sub>4</sub> represents a nitrogen atom or a group -CR<sub>7</sub> in which R<sub>7</sub> is selected from hydrogen, -NR<sub>8</sub>R<sub>9</sub>, -OR<sub>8</sub>, -SR<sub>8</sub>, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C<sub>5</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>10</sub>)heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl, these groups being optionally substituted by -(CH<sub>2</sub>)<sub>p</sub>-OH or -(CH<sub>2</sub>)<sub>p</sub>-NH<sub>2</sub> wherein p is an integer from 0 to 4 inclusive,

20           and in which R<sub>8</sub> and R<sub>9</sub>, identical or different, are selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl,

          and X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, R<sub>1</sub>, R<sub>2</sub>, A, Z, n and q are as defined hereinbefore.

25           optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

4- A compound according to claim 1 wherein :

W<sub>2</sub> represents a group selected from hydrogen atom, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl,

W<sub>1</sub> represents an oxygen atom or a sulfur atom,

5 X<sub>1</sub> represents a -CH group,

X<sub>2</sub> represents a -CH group or a nitrogen atom,

X<sub>3</sub> represents a -CH group,

and R<sub>1</sub>, R<sub>2</sub>, A, Z, n and q are as defined in formula (I),

optionally, its optical isomers , N-oxides, and addition salts thereof with a  
10 pharmaceutically-acceptable acid or base.

5- A compound according to claim 1 wherein :

W<sub>2</sub> represents a group selected from hydrogen atom, amino, mono(C<sub>1</sub>-C<sub>10</sub>)alkylamino, di(C<sub>1</sub>-C<sub>10</sub>)alkylamino, each alkyl moiety being identical or different, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)alkenyl, (C<sub>3</sub>-C<sub>6</sub>)alkynyl, (C<sub>5</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, and  
15 (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl,

W<sub>1</sub> represents an oxygen atom or a sulfur atom,

X<sub>1</sub> represents a nitrogen atom or a -CH group

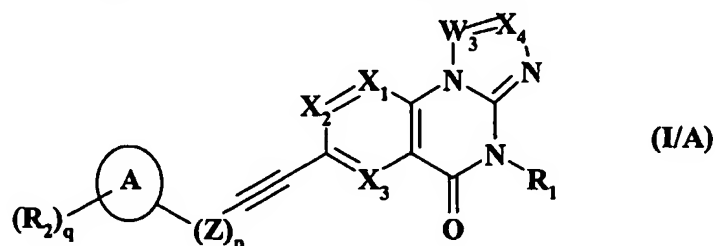
X<sub>2</sub> represents a -CH group,

X<sub>3</sub> represents a -CH group,

20 and R<sub>1</sub>, R<sub>2</sub>, A, Z, n and q are as defined in formula (I),

optionally, its optical isomers , N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

6- A compound according to claim 3 wherein it represents a compound of formula (IA) :



25 in which:

W<sub>3</sub> represents -CR<sub>5</sub> wherein R<sub>5</sub> represents a hydrogen atom or a methyl group,

$X_4$  represents a nitrogen atom or  $-CR_7$  wherein  $R_7$  represents a hydrogen atom or a methyl group,

$n$  is an integer from 1 to 4 inclusive,

and  $X_1$ ,  $X_2$ ,  $X_3$ ,  $R_1$ ,  $R_2$ ,  $A$ ,  $Z$  and  $q$  are as defined in the formula (I),

5 optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

7- A compound according to claim 1 wherein :

A represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzo-1,2,5-thiadiazolyl, 10 benzo-1,2,5-oxadiazolyl or indolyl,

$q$  is an integer from 0 to 4 inclusive,

the group(s)  $R_2$ , which may be identical or different, are selected from hydrogen,  $(C_1-C_6)$ alkyl, halogen, cyano, nitro, trihalogeno $(C_1-C_6)$ alkyl,  $-NR_{14}R_{15}$ ,  $-OR_{14}$ ,  $-SO_2R_{14}$ ,  $-(CH_2)_kSO_2NR_{14}R_{15}$ ,  $-X_5(CH_2)_kC(=O)OR_{14}$ ,  $-(CH_2)_kC(=O)OR_{14}$ ,  $-X_5(CH_2)_kC(=O)NR_{14}R_{15}$ , 15  $-(CH_2)_kC(=O)NR_{14}R_{15}$  and  $-X_6-R_{16}$  in which :

- $X_5$  represents an oxygen atom, a sulfur atom, or a  $-NH$  group,
- $k$  is an integer from 0 and 3 inclusive,
- $R_{14}$  and  $R_{15}$  identical or different represent hydrogen or  $(C_1-C_6)$ alkyl,
- $X_6$  represents an oxygen atom,
- 20 •  $R_{16}$  represents a phenyl group which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen, and hydroxyl,

and  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$ ,  $R_1$ ,  $Z$  and  $n$  are as defined in formula (I),

optionally, its optical isomers, N-oxides, and addition salts thereof with a 25 pharmaceutically-acceptable acid or base.

8- A compound according to claim 1 wherein :

A represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, and benzodioxolyl,

q is an integer from 0 to 4 inclusive,

the group(s)  $R_2$ , which may be identical or different, are selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, cyano, nitro, trihalogeno(C<sub>1</sub>-C<sub>6</sub>)alkyl, -NR<sub>14</sub>R<sub>15</sub>, -OR<sub>14</sub>, -SO<sub>2</sub>R<sub>14</sub>, -(CH<sub>2</sub>)<sub>k</sub>SO<sub>2</sub>NR<sub>14</sub>R<sub>15</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>14</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>14</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>14</sub>R<sub>15</sub>, and -(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>14</sub>R<sub>15</sub> in which :

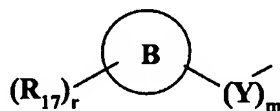
- X<sub>5</sub> represents an oxygen atom, a sulfur atom, or a -NH group,
- k is an integer from 0 and 3 inclusive,
- R<sub>14</sub> and R<sub>15</sub>, identical or different, represent hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl,

and W<sub>1</sub>, W<sub>2</sub>, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, R<sub>1</sub>, Z and n are as defined in formula (I),

optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

9- A compound according to claim 1 wherein :

R<sub>1</sub> represents hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl or the group of formula :



in which:

- m is an integer from 0 to 3 inclusive,
- Y represents -CR<sub>18</sub>R<sub>19</sub>, wherein R<sub>18</sub> and R<sub>19</sub> independently of each other, represent a group selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, and phenyl,
  - and when m is greater than or equal to 2, the hydrocarbon chain Y optionally contains one multiple bonds,
  - and/or one of the carbon atoms in the hydrocarbon chain Y may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted,
- B represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzo-1,2,5-thiadiazolyl, benzo-1,2,5-oxadiazolyl, naphthyl and indolyl,
- r is an integer from 0 to 3 inclusive,

- the group(s)  $R_{17}$  which may be identical or different are selected from hydrogen,  $(C_1-C_6)$ alkyl, halogen, cyano, nitro, trihalogeno $(C_1-C_6)$ alkyl,  $-NR_{14}R_{15}$ ,  $-OR_{14}$ ,  $-SO_2R_{14}$ ,  $(CH_2)_kSO_2NR_{14}R_{15}$ ,  $X_5(CH_2)_kC(=O)OR_{14}$ ,  $(CH_2)_kC(=O)OR_{14}$ ,  $X_5(CH_2)_kC(=O)NR_{14}R_{15}$ ,  $-(CH_2)_kC(=O)NR_{14}R_{15}$  wherein :

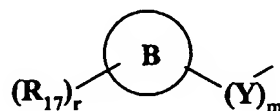
- 5
- $k$  is an integer from 0 to 3 inclusive,
  - $X_5$  represents an oxygen atom, a sulfur atom, or a group  $-NH$ ,
  - $R_{14}$  and  $R_{15}$ , identical or different, represent a hydrogen atom or a  $(C_1-C_6)$ alkyl group,

and  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$ ,  $R_2$ ,  $Z$ ,  $n$  and  $q$  are as defined in formula (I),

- 10 optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

**10-** A compound according to claim 1 wherein :

$R_1$  represents a group of formula :



- 15 in which:

- $m$  is an integer from 0 to 3 inclusive,
- $Y$  represents  $-CR_{18}R_{19}$ , wherein  $R_{18}$  and  $R_{19}$  independently of each other, represent a group selected from hydrogen and methyl,
  - and when  $m$  is greater than or equal to 2, the hydrocarbon chain  $Y$  optionally contains one double bonds,
  - and/or one of the carbon atoms in the hydrocarbon chain  $Y$  may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted,
- $B$  represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, and benzodioxolyl,
- $r$  is an integer from 0 to 3 inclusive,
- the group(s)  $R_{17}$  which may be identical or different are selected from hydrogen,  $(C_1-C_6)$ alkyl, halogen, cyano, nitro, trihalogeno $(C_1-C_6)$ alkyl,  $-NR_{14}R_{15}$ ,  $-OR_{14}$ ,  $-SO_2R_{14}$ ,

$(\text{CH}_2)_k\text{SO}_2\text{NR}_{14}\text{R}_{15}$ ,  $\text{X}_5(\text{CH}_2)_k\text{C}(=\text{O})\text{OR}_{14}$ ,  $(\text{CH}_2)_k\text{C}(=\text{O})\text{OR}_{14}$ ,  $\text{X}_5(\text{CH}_2)_k\text{C}(=\text{O})\text{NR}_{14}\text{R}_{15}$ ,  
 $-(\text{CH}_2)_k\text{C}(=\text{O})\text{NR}_{14}\text{R}_{15}$  wherein :

- k is an integer from 0 to 3 inclusive,
- $\text{X}_5$  represents an oxygen atom, a sulfur atom, or a group  $-\text{NH}$ ,
- 5        -  $\text{R}_{14}$  and  $\text{R}_{15}$ , identical or different, represent a hydrogen atom or a  $(\text{C}_1\text{-C}_6)$ alkyl group,

and  $\text{W}_1$ ,  $\text{W}_2$ ,  $\text{X}_1$ ,  $\text{X}_2$ ,  $\text{X}_3$ ,  $\text{R}_2$ ,  $\text{Z}$ ,  $n$  and  $q$  are as defined in formula (I),

optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

- 10        **11-** A compound according to claim 1 wherein  $n$  is equal to one, optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

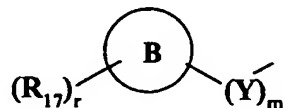
- 15        **12-** A compound according to claim 1 wherein  $\text{Z}$  represents a group  $-\text{CR}_{12}\text{R}_{13}$  in which  $\text{R}_{12}$  and  $\text{R}_{13}$  represent each a hydrogen atom, optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

**13-** A compound according to claim 1 wherein  $\text{A}$  represents a 5- to 6- membered aromatic monocycle optionally substituted by one or more groups  $\text{R}_2$  as defined in the compound of formula (I), optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

- 20        **14-** A compound according to claim 13 wherein  $\text{A}$  represents a phenyl group optionally substituted by one group  $\text{R}_2$  as defined in the compound of the formula (I), optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

- 25        **15-** A compound according to claim 13 wherein  $\text{A}$  represents a phenyl group and  $\text{R}_2$  represents a methoxy group, optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

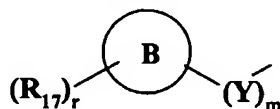
**16-** A compound according to claim 2 wherein  $W_2$  represents an oxygen atom,  $W_1$  represent a linear or branched ( $C_1$ - $C_6$ )alkyl group and  $R_1$  represent a group of formula :



in which Y, B,  $R_{17}$ , m and r are as defined in the compound of formula (I),

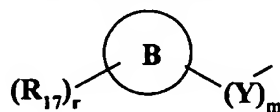
- 5 optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

**17-** A compound according to claim 16 wherein  $R_1$  represent a group of formula :



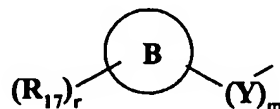
- 10 in which m is equal to one, Y represents a methylene group, B represents a phenyl group which is optionally substituted by one group  $R_{17}$  which represents a group  $(CH_2)_k-C(=O)OR_{14}$  in which k and  $R_{14}$  are as defined in the compound of formula (I), optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

- 15 **18-** A compound according to claim 3 wherein  $W_3$  represents a group  $-CR_5$  in which  $R_5$  is a hydrogen atom,  $X_4$  represents a nitrogen atom and  $R_1$  represents a group of formula :



in which Y, B,  $R_{17}$ , m and r are as defined in the compound of formula (IA), optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

- 20 **19-** A compound according to claim 18 wherein  $R_1$  represent a group of formula :



in which m is equal to one, Y represents a methylene group, B represents a phenyl group which is optionally substituted by one group  $R_{17}$  which represents a group

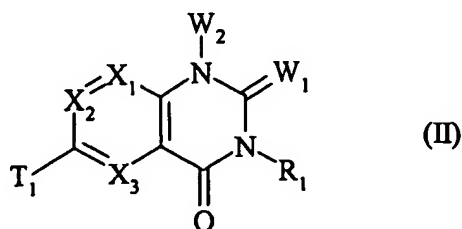


$-(CH_2)_k-C(=O)OR_{14}$  in which  $k$  and  $R_{14}$  are as defined in the compound of formula (IA), optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

**20-** A compound according to claim 1, which is selected from :

- 5 Methyl 4-{6-[3-(4-methoxyphenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate,  
4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid,  
4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid,  
10 4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid,  
4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl}-benzoic acid,  
15 4-Benzyl-7-(3-phenyl-prop-1-ynyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one,  
4-Benzyl-7-[(4-methoxyphenyl)-prop-1-ynyl]-4*H*-[1,2,4]-triazolo[4,3-*a*]quinazolin-5-one,  
Methyl 4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-4-ylmethyl}-benzoate,  
4-[5-Oxo-7-(3-phenyl-prop-1-ynyl)-5*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-4-ylmethyl]-  
20 benzoic acid,  
and 4-(1-Methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2*H*-quinazolin-3-ylmethyl)-benzoic acid.

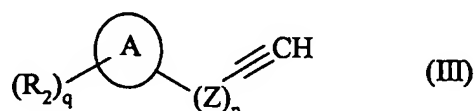
**21-** A process for the preparation of compounds according to claim 1 in which uses as starting material a compound of formula (II):



in which  $R_1$ ,  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$  and  $X_3$  have the same definitions as the compounds of formula (I), and  $T_1$  represents a group selected from hydrogen, halogen, mesylate, triflate, formyl, acetyl, and ester,

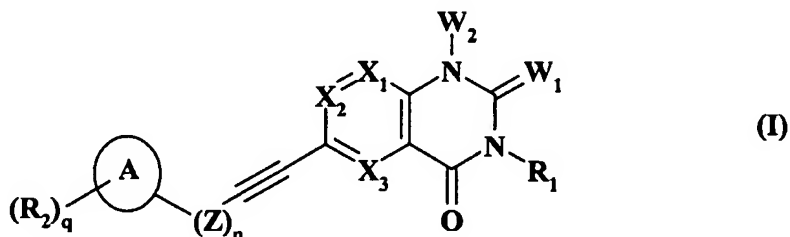
compound of formula (II) which is treated :

- 5     ❖ either when  $T_1$  represents an halogen atom, a mesylate group, or a triflate group, in the presence of a base under conditions of palladium-catalyzed alkynylation with a compound of formula (III):



in which A, Z,  $R_2$ , q and n are as defined for the compounds of formula (I),

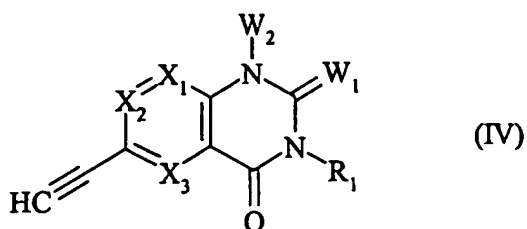
- 10    to yield the compounds of formula (I),



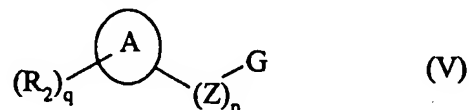
❖ or when  $T_1$  represents an hydrogen atom, with iodine to yield *in situ* the corresponding iodide intermediate, which is treated directly without isolation or purification, with a compound of formula (III) as described hereinbefore, under conditions of palladium-catalyzed alkynylation in the presence of a base,

15    to yield the compounds of formula (I),

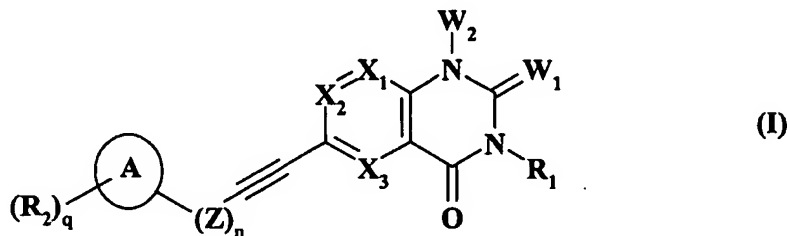
❖ or when  $T_1$  represents an acetyl group, first with lithium diisopropylamine at  $-78^\circ\text{C}$  in an inert solvent to provide an enolate, second with diethyl chlorophosphate and subsequently with lithium diisopropylamine, to yield a compound of formula (IV):



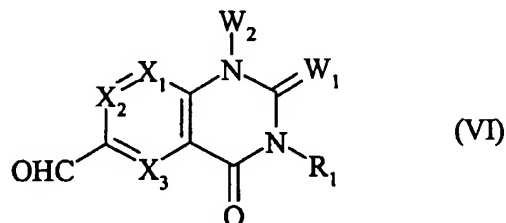
in which  $R_1$ ,  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$  and  $X_3$  are as defined hereinbefore,  
and condensing the compound of formula (IV), in the presence of triphenylphosphin and  $\text{PdCl}_2(\text{PPh}_3)_2$ , under basic conditions to a compound of formula (V):



- 5 in which A, Z,  $R_2$ , q and n are as defined hereinbefore and G represents a leaving group,  
to yield the compound of formula (I),



❖ or when  $T_1$  represents an ester group, with a reductive agent, to yield the  
corresponding aldehyde compound of formula (VI):



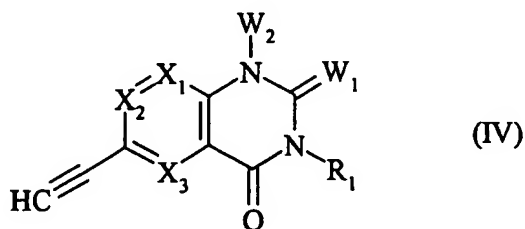
10

in which  $R_1$ ,  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$  and  $X_3$  are as defined hereinbefore,

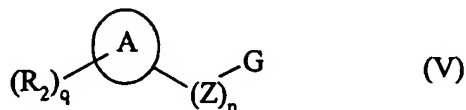
and subsequently :

- either condensing said compound of formula (VI), in basic conditions, with  
diazomethyl trimethyl silane or with diazomethyl diethoxy phosphonate, to yield,  
after basic treatment, a compound of formula (IV) as defined hereinbefore :

15



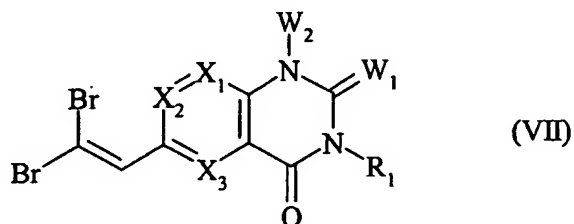
and adding said compound of formula (IV) to a compound of formula (V) as described hereinbefore :



in which  $R_2$ , A, Z, q, n and G are as defined hereinbefore,

to yield the compound of formula (I),

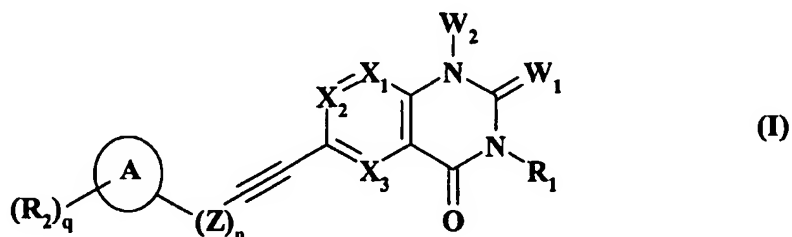
- or reacting, said compound of formula (VI), with tetrabromomethane in the presence of triphenylphosphine in an aprotic solvent to yield a compound of formula (VII) :



in which  $R_1$ ,  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$  and  $X_3$  are as defined hereinbefore,

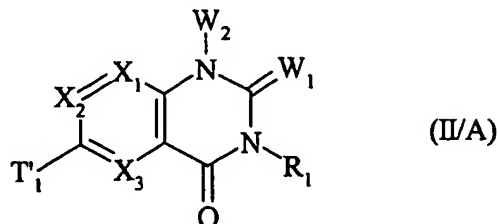
and dehalogenating said compound of formula (VII) through treatment with a strong base in an inert solvent, or with butyllithium in presence of triphenylphosphine and zinc, to yield the compound of formula (IV) as defined hereinbefore,

and reacting said compound of formula (IV) with a compound of formula (V) as defined in the previous step to yield a compound of a general formula (I):



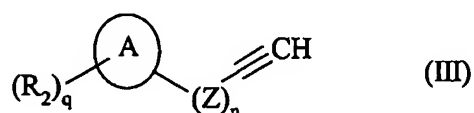
which constitute the compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base.

22- A process for the preparation of compounds according to claim 1 wherein it is used as starting material a compound of formula (II/A) :

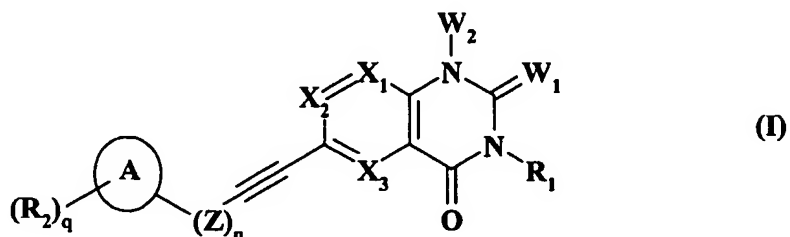


in which R<sub>1</sub>, W<sub>1</sub>, W<sub>2</sub>, X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> have the same definitions than in the compounds of formula (I), and T'<sub>1</sub> represents a group selected from halogen, mesylate, and triflate,

compound of formula (II/a) which is condensed, in the presence of dichlorobis(triphenylphosphine)palladium, copper iodide and *N,N'*-diisopropylethylamine in dimethylformamide, on a compound of formula (III):



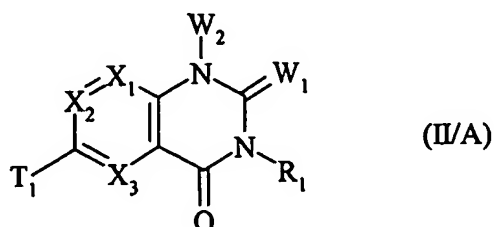
in which A, Z, R<sub>2</sub>, q and n are as defined in the compounds of formula (I), to yield the compounds of formula (I),



wherein W<sub>1</sub>, W<sub>2</sub>, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, R<sub>1</sub>, R<sub>2</sub>, A, Z, n and q are as described in claim 1.

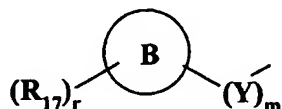
23- A process for the preparation of compounds according to claim 2 comprising the following step :

- reacting as starting material, a compound of formula (II/A) :



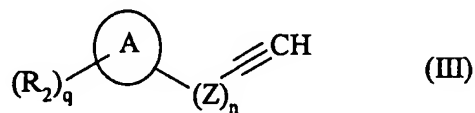
in which  $W_1$  represents an oxygen atom,  $W_2$  represents a  $(C_1-C_6)$ alkyl group,  $X_1$  represents a  $-CH$  group,  $X_2$  represents a nitrogen atom or a  $-CH$  group,  $X_3$  represents a  $-CH$  group, and  $T_1$  represent a iodine atom or a triflate group, and  $R_1$  represents a group of formula :

5



in which  $Y$  represents a methylene group,  $m$  is equal to one,  $B$  represents a phenyl group,  $R_{17}$  is as defined in the compound of formula (I) and  $r$  is equal to one,

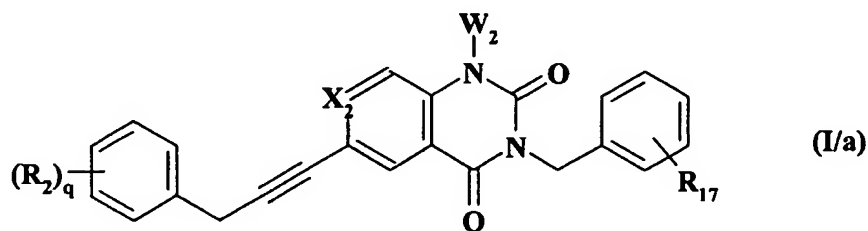
- with, as reagent, a compound of formula (III) :



10

in which  $Z$  represents a methylene group,  $n$  is equal to one,  $A$  is a phenyl group,  $q$  is equal to zero or one, and  $R_2$  is as defined in the compound of formula (I),

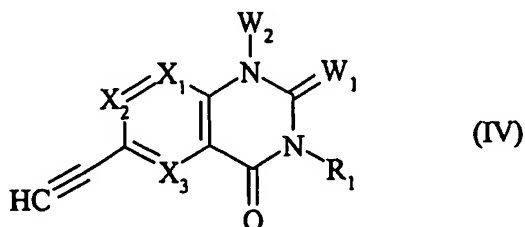
to yield a compound of formula (I/a), which constitutes a particular subgroup of the compounds of formula (I):



15

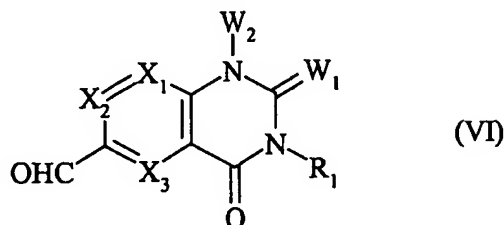
in which  $W_2$ ,  $X_2$ ,  $R_2$ ,  $q$  and  $R_{17}$  are as defined hereinbefore.

**24-** Intermediate compound of formula (IV) :



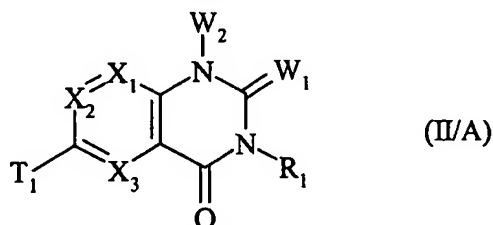
wherein  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$ ,  $R_1$  and  $R_2$  are as described in claim 1.

**25-** Intermediate compound of formula (VI) :



wherein  $W_1$ ,  $W_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$  and  $R_1$  are as defined in claim (I).

5      **26-** Intermediate compound of formula (II/A) :



wherein :

$W_1$  represents an oxygen atom, a sulfur atom, or a  $-NR_3$  group in which  $R_3$  represents hydrogen atom,  $(C_1-C_6)$ alkyl, hydroxyl or cyano,

10       $W_2$  represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono( $C_1-C_{10}$ )alkylamino, di( $C_1-C_{10}$ )alkylamino, each alkyl moiety being identical or different,
- $(C_1-C_6)$ alkyl,  $(C_3-C_6)$ alkenyl,  $(C_3-C_6)$ alkynyl,  $(C_5-C_{10})$ aryl,  $(C_5-C_{10})$ aryl( $C_1-C_{10}$ )alkyl,  $(C_3-C_{10})$ cycloalkyl( $C_1-C_{10}$ )alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected from halogen, amino, mono( $C_1-C_{10}$ )alkylamino, di( $C_1-C_{10}$ )alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno( $C_1-C_6$ )alkyl,  $(C_1-C_6)$ acyl,  $-C(=O)OR_4$ ,  $-OR_4$  and  $-SR_4$ ,  $R_4$  representing a hydrogen atom or a  $(C_1-C_6)$ alkyl group,

T<sub>1</sub> represents a halogen atom,  
and R<sub>1</sub>, X<sub>1</sub>, X<sub>2</sub>, and X<sub>3</sub> are as defined in the compounds of formula (I).

5     **27-** A method for treating a living body afflicted with a disease where the inhibition of type -13 matrix metalloprotease is involved, comprising the step of administering to the living body an amount of a compound of claim 1 which is effective for alleviation of said conditions.

10    **28-** A method for treating a living body afflicted with a disease selected from arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease, age-related macular degeneration, and cancers, comprising the step of administering to the living body an amount of a compound of claim 1 which is effective for alleviation of said conditions.

15    **29-** A pharmaceutical composition comprising as active ingredient an effective amount of a compound as claimed in claim 1, alone or in combination with one or more pharmaceutically-acceptable excipients or carriers.

**30-** A pharmaceutical composition useful in the method of Claim 28 comprising as active ingredient an effective amount of a compound as claimed in claim 1, together with one or more pharmaceutically-acceptable excipients or carriers.

20    **31-** A pharmaceutical composition useful in the method of Claim 28 comprising as active ingredient an effective amount of a compound as claimed in claim 2, together with one or more pharmaceutically-acceptable excipients or carriers.

25    **32-** A pharmaceutical composition useful in the method of Claim 28 comprising as active ingredient an effective amount of a compound as claimed in claim 3, together with one or more pharmaceutically-acceptable excipients or carriers.



**33-** A pharmaceutical composition useful in the method of Claim 28 comprising as active ingredient an effective amount of a compound as claimed in claim 20, together with one or more pharmaceutically-acceptable excipients or carriers.

5      **34-** Use of a compound according to Claim 1, for the preparation of a medicinal product intended for treating a disease involving therapy by inhibition of type-13 matrix metalloproteases.

10      **35-** Use according to Claim 33, characterized in that the disease is arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease, age-related macular degeneration, and cancers.

**36-** Use according to Claim 34, characterized in that the disease is arthritis.

**37-** Use according to Claim 34, characterized in that the disease is osteoarthritis.

**38-** Use according to Claim 34, characterized in that the disease is rheumatoid arthritis.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/11824

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/96 C07D487/04 A61K31/51 A61P19/02 C07D471/04  
 //(C07D471/04, 239:00, 221:00), (C07D487/04, 249:00, 239:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 818 819 A (E. C. TAYLOR, G. S. K. WONG) 4 April 1989 (1989-04-04) claim 9 ---	1-19
X	US 4 902 796 A (E. C. TAYLOR, G. S. K. WONG) 20 February 1990 (1990-02-20) claim 1 ---	1-19
X	US 5 646 141 A (M. D. VARNEY, W. H. ROMINES) 8 July 1997 (1997-07-08) * Compounds of formula V * --- -/--	1-38



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

18 March 2002

Date of mailing of the international search report

02/04/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax (+31-70) 340-3016

Authorized officer

Herz, C

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/11824

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 12, no. 1998, 31 October 1998 (1998-10-31) & JP 10 195063 A (DAIICHI SEIYAKU CO., LTD.), 28 July 1998 (1998-07-28) * Compounds of formula I * abstract ---	1-38
A	WO 00 44716 A (AMERICAN CYANAMID CO.) 3 August 2000 (2000-08-03) claims 1-16 ---	1-38
X	E. C. TAYLOR, P. S. RAY: "Pteridines. 51. A New and Unequivocal Route to C-6 Carbon-Substituted Pterins and Pteridines" J. ORG. CHEM., vol. 52, no. 18, 4 September 1987 (1987-09-04), pages 3997-4000, XP001062678 * Scheme I * ---	1-19
X	E. C. TAYLOR, G. S. K. WONG: "Convergent and Efficient Palladium-Effected Synthesis of 5,10-Dideaza-5,6,7,8-tetrahydrofolic Acid (DDATHF)" J. ORG. CHEM., vol. 54, no. 16, 21 July 1989 (1989-07-21), pages 3618-3624, XP001062654 * Compounds 14 & 15 * -----	1-19

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/11824

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4818819	A	04-04-1989	AT 104297 T	15-04-1994
			CA 1301157 A1	19-05-1992
			CA 1332169 A1	27-09-1994
			CA 1332170 A1	27-09-1994
			DE 3789599 D1	19-05-1994
			DE 3789599 T2	21-07-1994
			EP 0265126 A2	27-04-1988
			ES 2062985 T3	01-01-1995
			JP 2558086 B2	27-11-1996
			JP 8119968 A	14-05-1996
			JP 2069536 C	10-07-1996
			JP 7103120 B	08-11-1995
			JP 63183580 A	28-07-1988
			US 4988813 A	29-01-1991
			US 4902796 A	20-02-1990
US 4902796	A	20-02-1990	US 4818819 A	04-04-1989
			AT 104297 T	15-04-1994
			CA 1301157 A1	19-05-1992
			CA 1332169 A1	27-09-1994
			CA 1332170 A1	27-09-1994
			DE 3789599 D1	19-05-1994
			DE 3789599 T2	21-07-1994
			EP 0265126 A2	27-04-1988
			ES 2062985 T3	01-01-1995
			JP 2558086 B2	27-11-1996
			JP 8119968 A	14-05-1996
			JP 2069536 C	10-07-1996
			JP 7103120 B	08-11-1995
			JP 63183580 A	28-07-1988
			US 4988813 A	29-01-1991
US 5646141	A	08-07-1997	US 5608082 A	04-03-1997
			AT 206122 T	15-10-2001
			AU 697138 B2	24-09-1998
			AU 3151795 A	22-02-1996
			CA 2195420 A1	08-02-1996
			DE 69522945 D1	31-10-2001
			DK 773943 T3	04-03-2002
			EP 0773943 A1	21-05-1997
			ES 2162933 T3	16-01-2002
			FI 970317 A	05-03-1997
			JP 10503762 T	07-04-1998
			NO 970349 A	12-03-1997
			NZ 290703 A	25-11-1998
			RU 2152945 C2	20-07-2000
			SI 773943 T1	31-12-2001
			TW 432062 B	01-05-2001
			WO 9603406 A1	08-02-1996
JP 10195063	A	28-07-1998	NONE	
WO 0044716	A	03-08-2000	AU 2741700 A	18-08-2000
			BR 0007727 A	30-10-2001
			CN 1337947 T	27-02-2002
			EP 1149074 A1	31-10-2001
			NO 20013638 A	24-07-2001
			WO 0044716 A1	03-08-2000